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Anesthesia 101: What the Neonatologist Needs to Know About Anesthesiology

Amy E. Vinson, MD,* Walid Alrayashi, MD,* Constance S. Houck, MD, MPH*
**Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA*

Education Gaps

1. The doubling time for medical knowledge is now less than 3 months, leading to niche areas of expertise and challenging optimal communication among specialists, including anesthesiologists and neonatologists.
2. Medical students, pediatric residents, and neonatology fellows are not required to receive any formal training in anesthesiology, creating potential ambiguity for an entire field of medicine with which neonatologists frequently coordinate care.

Abstract

As the complexity of medicine increases, so too do the challenges with multidisciplinary communication and coordinated patient care. Anesthesiology represents a field for which there is no required study for medical students, pediatric residents, or neonatal-perinatal medicine fellows in the United States, so a neonatologist may have never received any formal training in anesthesiology (and vice versa for pediatric anesthesiologists in neonatology). In this review, we address frequently asked questions of neonatologists to anesthesiologists to better frame common issues. These topics include thermal regulation, fluid management, airway management, and the field of regional anesthesiology. Finally, collaborative efforts between the surgical and medical fields, such as the American College of Surgeons Children's Surgery Verification Quality Improvement Program, and the American Academy of Pediatrics NICU Verification Program, are ongoing and robust; these programs represent important opportunities to significantly improve the perioperative care of infants. Our hope is that this summary can serve as a primer and reference for those caring for neonatal patients during any perioperative period, including seasoned neonatologists and those early in their training. It is our further desire that this review will lead to improved communication and collegiality between the specialties.

Objectives

After completing this article, readers should be able to:

1. Explain the myriad factors involved in thermal and fluid regulation, unique to the operative environment, for neonatal patients.

AUTHOR DISCLOSURE Drs Vinson, Alrayashi, and Houck have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACS CSV	American College of Surgeons Children's Surgery Verification
ESP	erector spinae plane
ETT	endotracheal tube
HVLP	high volume low pressure
NMB	neuromuscular blockade
NSQIP-P	Pediatric National Surgical Quality Improvement Program
PV	paravertebral
SAD	supraglottic airway device
TIAE	tracheal intubation–associated event

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2. Describe the technical aspects salient to airway management and regional anesthesia, often used when neonates undergo operative procedures.
3. Recognize the potential role for improved communication between anesthesiologists and neonatologists, particularly surrounding clinical handovers.

INTRODUCTION

"Are we even speaking the same language?"

Each year medicine becomes more complex. It is estimated that by 2020, the doubling time for medical knowledge will be only 73 days. (1) To sustain this, physicians and other health care clinicians have become ever more specialized in niche areas of expertise. As with any human grouping, within each niche is a cohesive sense of community and language to navigate their daily tasks. Clinicians within each field (ie, neonatology or anesthesiology) speak among themselves with a fluent set of 3-letter acronyms and shared background. It is not surprising then that, with the exception of medical polyglots, miscommunications and misunderstandings are common.

On initial inspection, there are many differences between the worlds of anesthesiology and neonatology. Anesthesiologists generally are involved in a relatively brief and discreet clinical interaction with the patient, while neonatologists provide one of the most longitudinal in-hospital care relationships. Anesthesiologists provide dynamic care during extraordinarily rapidly evolving and shifting physiologic events (ie, surgeries), while neonatologists are expert in stabilizing and finely adjusting exquisite homeostasis for profoundly compromised premature infants. Anesthesiologists work in an isolated and unusually autonomous clinical environment (eg, they are likely the only clinicians in the hospital who singularly order, draw up, and administer medications without any cross checks), while neonatologists work in one of the hospital's most collaborative decision-making environments.

Although these specialties have different languages, distinct environments, and a different evolution in practice, it can be argued that both pediatric anesthesiology and neonatology hold their origins and advancements in our reliance on, and fostering of, technological innovations. Furthermore, the sickest infants will often find themselves in the care of these 2 highly trained subspecialists, so improved communication and collaboration can have a high yield for improved patient care.

We begin this review—this primer on neonatal anesthesia—with our assumptions regarding anesthesiologists and neonatologists:

- Anesthesiologists are highly trained, intelligent, and capable physicians who care deeply for their patients.
- Neonatologists are highly trained, intelligent, and capable physicians who care deeply for their patients.

Although it may seem simplistic, this place of fundamental grounding is a good place to start in describing the rationale for the anesthesia care provided to neonatal patients. In a study of emergency medicine and hospital medicine physicians, the authors found that actively promoting interdisciplinary communication and understanding led to enhanced collaboration and a "shared mental model" of patient care. (2)

This review is organized by a series of frequently asked questions (and sometimes frustrations) that have been shared with us by neonatologists. We will address intraoperative thermoregulation, fluid management, and regional anesthesia. We will discuss airway management, exploring both equipment used and clinical strategies for success. Finally, we will discuss multidisciplinary handovers, coordinated care, and implementation of the American College of Surgeons Children's Surgery Verification (ACS CSV) NICU standards and the AAP NICU Verification Program. All authors of this review are pediatric anesthesiologists, 2 are pediatricians with extensive experience in critical care and neonatal-perinatal medicine, and 1 has extensive experience in pediatric regional anesthesia.

THERMAL REGULATION

"Is it really so hard to keep them warm?"

Volatile anesthetics (eg, isoflurane, sevoflurane, nitrous oxide), intravenous anesthetics (eg, propofol), and opioids all impair thermoregulatory control. (3) The primary mechanism for this effect is reduction in the threshold for vasoconstriction to approximately 34.5°C. All patients receiving anesthetics have a poikilothermic response to ambient temperatures over a much broader range of core temperatures and easily become hypothermic during surgery. Moreover, anesthesia also impairs nonshivering thermogenesis in infants. (4) Therefore, infants undergoing both surgical and noninvasive procedures requiring general anesthesia are at particular risk for periprocedural hypothermia. Even mild hypothermia can

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contribute to perioperative morbidity and mortality. Randomized trials in anesthetized adults have demonstrated that mild perioperative hypothermia can interfere with the pharmacodynamics of anesthetic agents (especially nondepolarizing muscle relaxants), increase surgical site infections, reduce clot formation, and increase blood loss. (3)(5)

A recent study of more than 50,000 adult patients undergoing noncardiac surgery at the Cleveland Clinic demonstrated that after the induction of general anesthesia, core temperature dropped rapidly, because of a balancing of the "cold" peripheral thermal compartment and the "warm" core thermal environment (Fig 1). (6) This shift is a result of the vasodilation caused by anesthetic agents and results in rapid redistribution of heat rather than overall heat loss. Infants are particularly vulnerable to this initial drop in core temperature during the first hour of anesthesia for a number of reasons. Infants have a greater body surface-to-volume ratio (preterm infants have a ratio nearly 4 times that of adults and full-term infants 3 times that of adults). (7) In addition, infants are often uncovered for the first 30 to 60 minutes after induction of anesthesia for the placement of invasive lines, such as additional peripheral intravenous lines, peripherally inserted central catheters, and arterial catheters. Though operating rooms can often be warmed before the infant's arrival, many environments in which infants receive anesthesia, such as the magnetic resonance imaging suite, are maintained at cooler temperatures that allow for the proper functioning of the imaging equipment leading to significant convective heat loss. Warming of the skin using forced air is the most effective way to reduce this initial drop in temperature during the early period of general anesthesia. For this method to be effective, however, the forced-air blankets must be placed directly on the patient's skin and cover as much of the body as possible. (8) Though overhead heat lamps can be used to reduce heat loss when infants are uncovered for line placement, these lights sometimes interfere with line placement and are turned off or removed.

Passive insulation with blankets or head coverings can reduce heat loss but do not add heat and are not effective in maintaining perioperative normothermia. Active forms of warming are needed to counteract the thermoregulatory effects of anesthetics. There are several methods of active warming, but skin warming with forced air is the most effective; the earlier it is introduced in the perioperative period, the more effective it is in reducing perioperative hypothermia. (8) Other methods of active warming, such as fluid warming and warming of inspired gases, are not as effective. Fluids can only be warmed to 38°C to 39°C and this method is not effective for active warming unless large volumes of fluids are given over a short period. The reduction in heat loss can be significant, however, compared with administering fluids to infants at room temperature. Warming of inspired gases and the use of low fresh gas flow rates also reduce heat loss but are not particularly effective at providing active warming. Despite the routine use of continuous monitoring of core temperature throughout the perioperative period and the use of both passive and active warming methods, maintaining core temperature during both invasive and noninvasive procedures in infants under general anesthesia can be particularly challenging (as described in the following section).

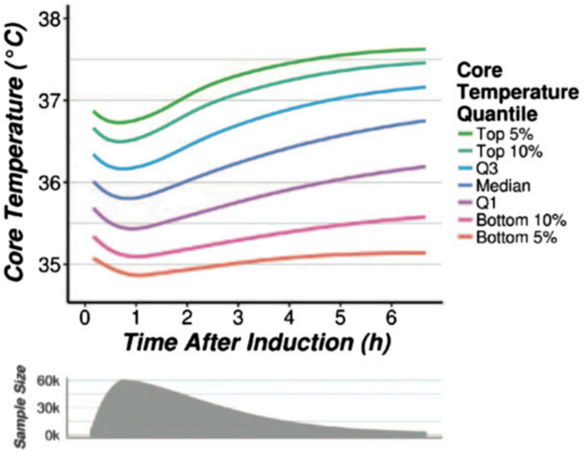

Figure 1. Distribution of core temperature as a function of time after induction. Reprinted with permission from Sun Z, Honar H, Sessler DI, et al. Intraoperative core temperature patterns, transfusion requirement, and hospital duration in patients warmed with forced air. *Anesthesiology*. 2015;122:276–285. (6)

FLUID MANAGEMENT IN THE OPERATING ROOM

"Are you trying to drown them?"

One of the defining features of perinatal care is the intricate and calculated management of fluid, from urine output to daily weights to total daily intravenous fluids. That lies starkly juxtaposed to the relatively higher intravenous fluid administration often required during an operative procedure; so it is understandable that misunderstandings often arise regarding perioperative fluid administration. It would be naïve to state that all anesthesiologists unfailingly and meticulously deliver only as much intravenous fluid as is absolutely required during their care. However, it is equally unreasonable to apply the same fluid management guidelines to the operative environment as to the NICU environment, for several reasons, which we will explore further here.

In addition to the administration of a standard rate of maintenance or total daily fluids, the fluid dynamics encountered during administration of an anesthetic are

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of 2 major categories: changes in the quantity of intravascular fluid and changes to the capacitance of the intravascular system (ie, the ability of the vascular system to change the volume of blood it is able to hold). (9) The quantity of intravascular fluid can change via evaporative loss, translocated ("third spaced") fluid or blood loss, or can be initially in a deficit state because of perioperative fasting (rarer in the neonatal population). The capacitance of the intravenous system can increase dramatically via an inflammatory response or, most commonly, as a normal vascular response to anesthetic agents. Finally, certain forces can affect cardiac preload, necessitating a fuller than usual fluid status to maintain optimal cardiac function. These forces include positive pressure ventilation and exogenous mechanical pressure from the surgical team or instruments.

To best understand the differences between the NICU and operative environment, gastroschisis is a particularly illustrative example. When treating an infant with exposed bowel, the first inclination of the neonatologist is to cover the bowel to limit evaporative and heat losses, which can be profound in the NICU environment. In the operative environment, however, this bowel must often be left uncovered for extended periods and in an environment conducive to much greater heat and evaporative losses. Even during laparoscopic surgery, the flow rates of insufflated carbon dioxide can generate significant evaporative fluid loss.

The ambient airflow in an operative environment is unique in a hospital setting. In an effort to minimize exposure to, among other things, waste anesthetic gases, the United States Occupational Safety and Health Administration recommends that, in an operating room, air must be exchanged at least 15 times per hour, (10) greatly increasing evaporative losses experienced, especially while a large surface area of skin or bowel is exposed. To visualize how this is accomplished, one only need look up in an operating room to observe the large number of stippled ceiling tiles covering large ventilation ducts. The dynamics of heat and fluid loss during the anesthetic course cannot be wholly uncoupled. Twenty-two percent of heat loss occurs through evaporation, so attention to evaporative fluid losses serves a dual role in the maintenance of physiologic equilibrium intraoperatively. (11)

In addition to fluid loss, the capacitance of the intravascular system often changes significantly during an anesthetic course. For example, in the case of necrotizing enterocolitis, infants often exhibit a systemic inflammatory response syndrome, characterized in part by systemic vasodilation. (12) With intraoperative manipulation of the bowel, inflammatory mediators are further released, often dramatically enhancing this response and concomitant vasodilation. Vasodilation is further exacerbated by the administration of anesthetic agents, most of which reliably cause a degree of decreased vascular tone or myocardial depression. (13)

Physiologically, one of the most dramatic perioperative events is the transition from awake resting negative pressure (spontaneous) ventilation to the initiation of positive pressure ventilation. The effects on fluid dynamics cannot be underestimated. Not only does the pressure in the right atrium increase, thereby decreasing venous return, but the increased venous pressure increases transcapillary pressure, causing a degree of interstitial fluid sequestration. (14)

When encountering this collective state of actual and relative fluid deficits, the anesthesiologist must balance the use of exogenous fluid administration and vasoactive medications to maintain an adequate end-organ tissue perfusion, often necessitating tremendous volumes of resuscitative fluid.

NEONATAL REGIONAL ANESTHESIA

"Can you place an epidural that doesn't leak?"

Regional anesthesia has been demonstrated to be safe in children and neonates and is increasingly being used as a part of multimodal perioperative analgesia. (15)(16) Although neonatologists may have some familiarity with caudal blocks and epidurals, the field of regional anesthesiology has dramatically changed in the last 10 years through improved techniques and the proliferation of a wide range of peripheral nerve blocks. (17)(18) Understanding the types, indications, contraindications, and techniques of placing regional anesthetic blocks is critical in maximizing the associated benefits and minimizing risk. Here we will explore the various types of regional anesthetics, including neuraxial, paraneuraxial, and peripheral blocks for intraoperative anesthesia/analgesia and postoperative pain control.

Neuraxial Blocks

The language of neuraxial blocks describes where the local anesthetics are deposited within or adjacent to the spinal canal. A "spinal" denotes placement of the local anesthetic in the intrathecal space, an "epidural" means that the local anesthetic is deposited into the epidural space just outside the dura (usually in the lumbar or thoracic region), and a "caudal" generally denotes that the local anesthetic is injected into the sacral epidural region via the easily palpated "sacral hiatus," a natural opening in the sacrum.

In neonates, a spinal is usually performed in the lumbar spaces L5-S1 or L4-5 as an anesthetic for inguinal hernia or other lower abdominal procedures. This is often performed to avoid general anesthesia, which is known to increase the

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risk for postoperative apnea and bradycardia. Generally, when a successful spinal is performed, the neonate is rendered immobile and insensate from the abdominal dermatomes down, depending on the local anesthetic spread, with the respiratory function unaffected. This creates acceptable surgical conditions for short duration procedures (generally <90 min) from the umbilicus to the perineal area. (19)

A spinal anesthetic is performed with the patient immobilized in the lateral or sitting position. A spinal needle is introduced into the appropriate interspinous level. It is recommended that a closed tip pencil point spinal needle with the smallest caliber is used to reduce postdural puncture leak (Fig 2B). Once the intrathecal space is accessed, a local anesthetic is injected. The patient is then quickly positioned in the supine position, taking great care not to raise the patient's legs above the level of the heart or tilt the patient in a Trendelenburg (head down) position. Doing so can result in cephalad spread of the local anesthetic resulting in a "total spinal" with subsequent apnea, bradycardia, and/or cardiac arrest. Because of the rapid cerebrospinal fluid turnover in infants (generally 3 times that of adults), a spinal anesthetic generally provides no more than 60 to 90 minutes of acceptable operative conditions, depending on the local anesthetic medication used. In contrast to adults who often experience significant hypotension with interruption to the sympathetic chain, most neonates do not experience significant hemodynamic perturbations because of the immature development of the sympathetic system. (20)

Epidurals produce dense localized analgesia and can decrease the intraoperative inflammatory response, reduce the requirement for postoperative ventilation, and minimize the use of opioid-based pain medications. (19) Because of the lack of subcutaneous tissue over the sacral region and the distance from the dural sac, caudal blocks via the sacral hiatus remain among the simplest and safest regional blocks performed by pediatric anesthesiologists.

Single-shot caudal blockade is frequently performed in infants undergoing perineal, lower abdominal, or orthopedic procedures. A recent analysis of 18,650 caudal blocks performed in 20 different sites in the United States as part of the Pediatric Regional Anesthesia Network demonstrated no long-term sequelae with this block and a very low rate (upper incidence limit of 0.02%) of severe complications, such as cardiac arrest and seizure.(21) "Kiddie caudals" are generally easy to perform and can significantly reduce general anesthetic requirements and, when combined with acetaminophen and nonsteroidal anti-inflammatory agents, can completely eliminate the need for postoperative opioid analgesics. They have also been used as an alternative to spinal block for inguinal hernia repair in infants.

Details of the anatomic landmarks and placement of this block can be found in Fig 3. Entry in the caudal epidural space is through a defect in the lower part of the posterior wall of the sacrum (the sacral hiatus), formed by the failure of the laminae of S5 and usually part of S4 to meet and fuse in the median plane. This leaves a space of variable dimension, often described as an inverted U or V covered with a thick fibrous posterior sacrococcygeal ligament. Penetration of this ligament by a needle yields direct access to the caudal limit of the epidural space in the sacral canal.

Epidural catheters can be placed through thoracic, lumbar, and caudal routes depending on the location of the surgery and the areas to be anesthetized. For direct placement via the lumbar or thoracic routes using general anesthesia or sedation, the infant is placed in the lateral position. A hollow needle with a blunt curved tip, known as a Tuohy tip needle (Fig 4), is then carefully advanced using a loss of resistance to saline technique. In this approach, small advances are made while checking the plunger of the

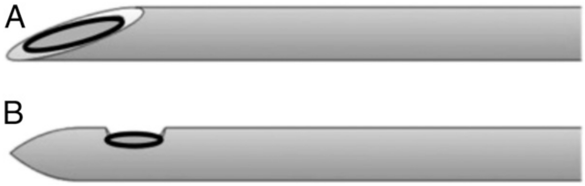

Figure 2. Two general types of spinal needles. A. Typical cutting needle. B. "Pencil-point" spinal needle.

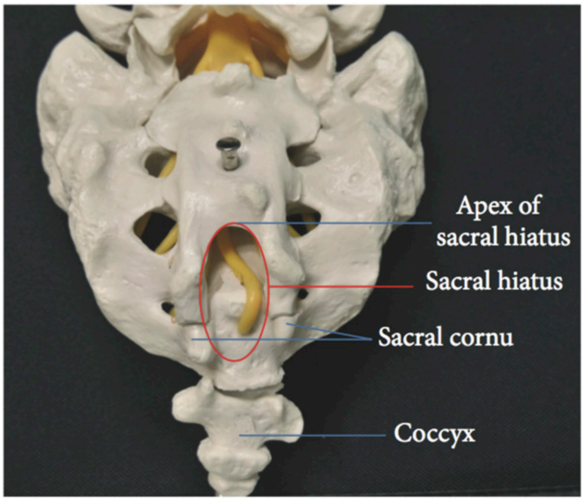

Figure 3. Anatomic landmarks for the placement of a caudal epidural neuraxial block. Reprinted with permission from Kao S-C, Lin C-S. Caudal epidural block: an updated review of anatomy and techniques. *Biomed Res Int Hindawi.* 2017;2017(5):9217145.

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syringe until a noticeable "pop" is felt upon penetrating the ligamentum flavum, coinciding with the syringe plunger easily allowing injection of saline. A smaller-gauge catheter is then placed into the lumen of the needle and advanced several centimeters (2–5 cm) beyond the tip of the needle into the epidural space. The needle is then removed and the catheter is tested to confirm appropriate placement. Initially, a syringe is connected and aspirated to ensure that no blood or cerebrospinal fluid is present. To further ensure that the catheter is not intravascular, a test dose of 1:200,000 epinephrine solution is injected into the catheter (0.15 mL/kg), and the electrocardiogram tracing is examined for changes in the T wave, QRS complex, or ST wave that might indicate intravascular injection. Confirmation of the location of the catheter tip using fluoroscopy is also recommended, which can frequently be coordinated with radiographs needed for other parts of the procedure.

Though direct placement of an epidural catheter at the lumbar or thoracic level is preferable when coverage of specific dermatomes is needed, high lumbar and thoracic level placement in small infants can increase the risk of spinal cord injury. Bösenberg and colleagues first demonstrated in the late 1980s that a catheter could be reliably threaded to the thoracic region from a caudal approach in neonates and young infants. (22) This technique allows neonates to have thoracic-level epidural analgesia using the simpler caudal approach. This "caudal to thoracic" catheter technique has a high success rate (>70%) in infants less than 5 kg. Because placement of the tip of the catheter at or near the spinal levels innervating the surgical site is crucial for the efficacy of this form of analgesia, the tip position should be routinely confirmed with radiography. (23) This may be done with a simple radiograph if a radio-opaque catheter is used or by the injection of radio-opaque dye through the catheter. For the latter, a small amount (0.5 mL) of myelogram-safe dye is used to ensure optimum placement in the desired level of epidural space. Ultrasound imaging of the spine is also becoming a popular method for confirming catheter position in neonates. (24) Both radiographic and ultrasonographic imaging modalities can also be used for initial needle placement and positioning, but this is not routine.

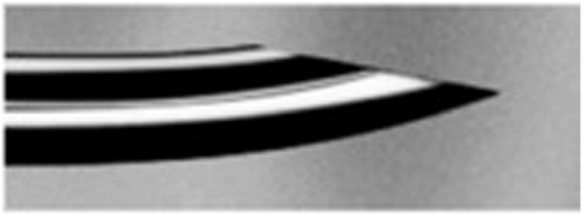

Figure 4. Tuohy tip epidural needle.

Leakage and dislodgement of the epidural catheter are a risk and attempts should be made to secure the catheter well. For example, one can use tissue adhesives, such as 2-octylcyanoacrylate, reinforced dressing, and/or specialized fixation devices. (25) An important consideration with caudal catheter placement is that it is in close proximity to the anus, so it may become contaminated with fecal matter. For this reason, anesthesiologists will sometimes tunnel the catheter beneath the skin to a more cephalad location away from the diaper area, reducing the risk of infection. (26)

One final pragmatic note is that, because epidural placement is performed via a catheter-through-needle technique, the access hole is larger than the retained catheter, in contrast to intravenous access, which is usually a catheter-over-needle technique. Because of this and the lack of absorptive subcutaneous tissue in small infants, it should be expected that epidural catheters will often leak. Leakage at the site of epidural insertion should, therefore, *not* be immediately regarded as a sign of a malfunctioning block. The radiograph in Fig 5 shows the path of contrast dye in the epidural space of a 5-month old infant, demonstrating tracking of the dye back along the path of the catheter and accumulating beneath the dressing. (27)

Paraneuraxial Blocks

The field of regional anesthesia has continued to grow with more novel approaches to improve postoperative analgesia and reduce opioid use. These include paravertebral (PV) and erector spinae plane (ESP) blocks. These blocks are used as an alternative when neuraxial blockade is either absolutely or relatively contraindicated, such as thoracic surgery requiring prolonged postoperative sedation or muscle relaxation where a neurologic examination cannot reliably be conducted. Neurologic examination is the key method of ensuring an epidural hematoma has not occurred when an epidural is performed. PV blocks are typically performed using ultrasonography with the aim of depositing local anesthetic around the sympathetic and intercostal nerves that course through this PV space. (28) Given the proximity to the pleura and central canal, cases of pneumothoraces and hypotension have been reported with these blocks, though both are rare. (29)

ESP blocks are quickly gaining popularity owing to the lower risk of bleeding and ease of placement. (30) In fact, these blocks are under investigation for use in patients after cardiac surgery, who often have postoperative anticoagulation. (31) These blocks are performed by depositing local anesthetic between the erector spinae muscle and the transverse process at the desired dermatomal level. (32)

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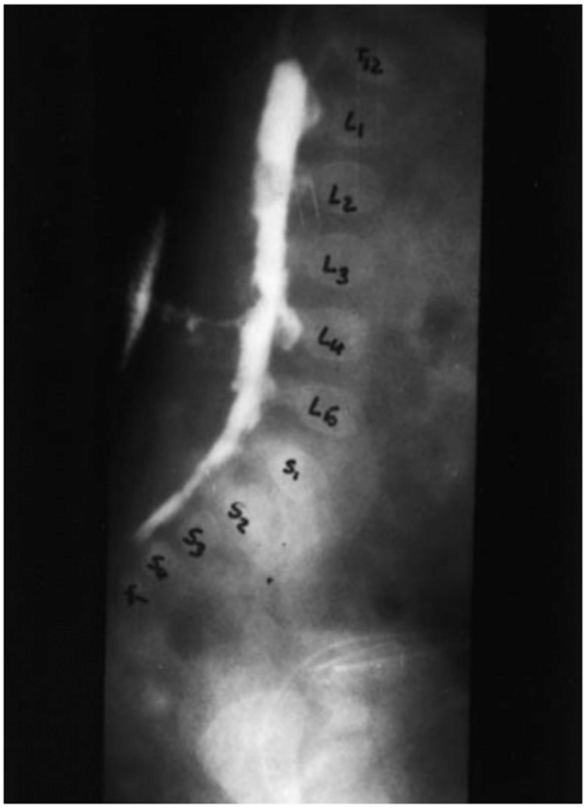

Figure 5. Epidural leakage in infants. This radiograph demonstrates an epidurogram in a 5-month-old infant obtained after injection of 0.5 mL/kg of contrast dye at 1 mL/2 min, illustrating the spread of the dye not only within the epidural space but also back along the track of the needle, collecting beneath the dressing. Adapted with permission from Vas L, Raghavendran S, Hosalkar H, Patil B. A study of epidural pressures in infants. *Paediatr Anaesth*. 2001;11:575–583. (27)

Peripheral Blocks

Although uncommon, peripheral nerve blocks can be placed in neonates after procedures involving the extremities. Herein local anesthetics are deposited around a specific nerve or nerve group, such as the femoral nerve or brachial plexus. These blocks were traditionally performed in adults when awake as a safety measure so that a neurologic examination could be continuously performed to avoid potential nerve injury. However, with advances in ultrasonography technology and clinical practice, practitioners have been able to safely conduct these blocks in pediatric patients using general anesthesia. (15)(16)

Regional Anesthesia Medications

Local anesthetics commonly used for neuraxial and peripheral nerve blocks include bupivacaine, ropivacaine, tetracaine, and chloroprocaine. For single shot spinal anesthetics, either bupivacaine or tetracaine are used and dosed at 0.6 to 1 mg/kg for infants under 4 kg. Caudal epidural single injections consist of bupivacaine 0.25% or ropivacaine 0.2% solutions with a typical maximum dose of 1 mL/kg. (33)

One special consideration in infants, and especially neonates, is that they have lower levels of alpha-1-glycoprotein, which actively binds plasma local anesthetics. This results in a higher free fraction of local anesthetics. Therefore, it is generally recommended to reduce the dosage of all local anesthetics by 30% compared with children older than 6 months. Another option is to use chloroprocaine, which is dependent on neither hepatic metabolism nor renal clearance, which are both underdeveloped in infants. Because chloroprocaine is rapidly broken down by plasma esterases, the likelihood of local anesthetic toxicity during long infusion periods is reduced. (34)

For single-shot injections in peripheral nerve blocks, it is generally recommended to use 0.5 to 1.5 mg/kg of ropivacaine, levobupivacaine, or bupivacaine. Continuous-infusion epidural or peripheral nerve blocks are usually administered between 0.1 and 0.5 mg/kg per hour, depending on the age and type of local anesthetic, with younger infants generally receiving lower rates of infusion because of slower clearance. (35)

AIRWAY MANAGEMENT IN THE OPERATING ROOM

"What is your obsession with cuffed tubes?"

Whether for primary pulmonary dysfunction, secondary to hemodynamic instability, or to facilitate procedural intervention, airway securement via endotracheal intubation for a surgical procedure is common in the neonatal population. Although anesthesiologists and neonatologists generally have the same endpoint, the method of airway securement and the equipment used can often diverge significantly. It is important to understand the rationale behind the choices made by anesthesiologists to smooth perioperative care transitions.

One of the clearest differences between airway management by anesthesiologists and neonatologists is the use of cuffed or uncuffed endotracheal tubes (ETTs) and the methods of pharmacologic facilitation of intubation. Anesthesiologists must maintain complete control of ventilation through dynamic shifts in airway compliance, as well as guard against an increased probability of gastric reflux from direct manipulation of bowel. For this reason, many anesthesiologists opt for cuffed ETTs in the care of neonatal patients.

Cuffed versus Uncuffed ETTs

Thomas et al reviewed the use of cuffed versus uncuffed ETTs in the neonatal population and outlined their principal reasons for and against each approach. (36) With "some

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body of evidence," they contend that cuffed tubes decrease reintubation rates, decrease clinically significant ventilator leaks, and decrease aspiration and ventilator-associated pneumonia. They also speculate about other non–evidence-based benefits as well as disadvantages. (36) Of note, these comparisons were made using high volume low pressure (HVLP) ETTs, specifically a microthin polyurethane cuff ETT, which has the benefit of a more distally placed, lower pressure balloon, but lacks the Murphy eye often present at the distal tip of traditional ETTs.

A recent retrospective observational study of the use of HVLP cuffed ETTs in a pediatric intensive care unit population found an incidence of 0.68% clinically significant subglottic stenosis after intubation with cuffed tubes. In fact, the only infants requiring surgical correction of subglottic stenosis were neonates who underwent initial intubation with uncuffed ETTs in external NICUs. (37) Another retrospective cohort study, looking only at infants less than 3 kg, compared those intubated with HVLP ETTs versus uncuffed ETTs. All of the infants with HVLP ETTs were intubated in the operating room and subsequently had the cuff deflated in the NICU for further care, but there was no difference in ventilator parameters or incidence of postextubation stridor. (38)

If a cuffed ETT is used, careful attention must be given to the pressure in the pilot balloon, meticulously ensuring that cuff pressure remains at the minimal level to provide adequate ventilation. In fact, Dullenkopf et al demonstrated excellent tracheal seal with a cuff pressure less than 15 cm H_2O in 95% of children using microthin polyurethane cuff ETTs. (39) Monitoring of ETT cuff pressure represents a deviation from the standard practice in most NICUs, so greater use of these ETTs could represent a change in care flow and practice.

Supraglottic Airway Devices

Although the routine use of supraglottic airway devices (SADs), including laryngeal mask airways, is uncommon in NICUs, anesthesiologists are very familiar with their use. SADs are rarely used in first-line management of respiratory failure in neonates but can be useful for rescue during resuscitation when endotracheal intubation has failed or is unavailable. They are being used more frequently in the delivery room. A 2013 meta-analysis by Schmolzer et al found that use of a SAD during resuscitation led to fewer intubations or unsuccessful resuscitations. Given the available sizes of common SADs (Table 1), the authors argue that for infants of more than 2,000 g birthweight and 34 weeks' gestation, the use of a SAD is a reasonable alternative to bag mask ventilation during neonatal resuscitation. (40) The feasibility of use in a resource-poor environment has also been demonstrated in a randomized control trial in a Ugandan labor and delivery ward. (41)

Variations in Practice: Videolaryngoscopy and Pharmacologic Premedication

In an ongoing international registry study, investigators evaluated more than 2,000 intubations in the NICU and delivery room at 10 sites, seeking to identify factors associated with tracheal intubation–associated events (TIAEs). Tracheal intubation in the NICU and delivery room yielded

TABLE 1. **Common Supraglottic Airway Device (SAD) Brands and Sizes**

SAD DEVICE	DEVICE SIZE AND PATIENT WEIGHT
i-gel^{TM} (Intersurgical Ltd, Wokingham, UK): Cuffless SAD	• Size 1.0, neonate, 2–5 kg • Size 1.5, infant, 5–12 kg
LMA Supreme^{TM} (The Laryngeal Mask Company Pte Ltd, Singapore): includes suction port for orogastric suctioning	• Size 1, neonate/infant, up to 5 kg • Size 1.5, infants, 5–10 kg • Size 2, infants, 10–20 kg
LMA ProSeal^{TM} (Teleflex Medical Europe Ltd, County Westmeath, Ireland): Built-in drain allows gastric contents to bypass pharynx	• Size 1, neonate/infant, up to 5 kg • Size 1.5, infants, 5–10 kg • Size 2, infants, 10–20 kg
LMA Unique^{TM} and Classic (Teleflex)	• Size 1, neonate/infant, up to 5 kg • Size 1.5, infants, 5–10 kg • Size 2, infants, 10–20 kg
Air-Q (Cookgas, St Louis, MO): Facilitates intubation through SAD techniques	• Size 0.5, <4 kg • Size 1.0, 4–7 kg • Size 1.5, 7–17 kg

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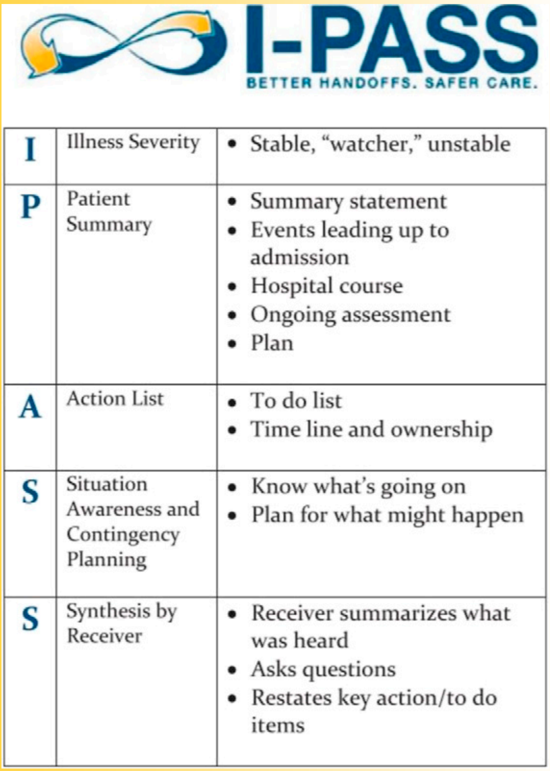
TABLE 2. **Elements of the I-PASS Mnemonic**



I-PASS
BETTER HANDOFFS. SAFER CARE.

I	Illness Severity	• Stable, "watcher," unstable
P	Patient Summary	• Summary statement • Events leading up to admission • Hospital course • Ongoing assessment • Plan
A	Action List	• To do list • Time line and ownership
S	Situation Awareness and Contingency Planning	• Know what's going on • Plan for what might happen
S	Synthesis by Receiver	• Receiver summarizes what was heard • Asks questions • Restates key action/to do items

Adapted with permission from Starmer AJ, Spector ND, Srivastava R, Allen AD, Landrigan CP, Sectish TC; the i-PASS Study Group. I-PASS, a mnemonic to standardize verbal handoffs. Pediatrics. *2012;129;201–204.*

a 49% and 46% first attempt success rate, respectively, with a TIAE rate of 18% and 17% and a severe desaturation rate of 48% and 31%, respectively. The use of paralytic premedication was independently associated with a reduction in TIAEs (adjusted odds ratio [OR] 0.38, 95% confidence interval [CI] 0.25–0.57), as was the use of videolaryngoscopy (adjusted OR 0.46, 95% CI 0.28–0.73). (42) This registry illustrates both the use of videolaryngoscopes and pharmacologic premedication to facilitate endotracheal intubation; however, caution with neuromuscular blockage should be exercised in the presence of features suggestive of a difficult airway.

A videolaryngoscope is a laryngoscope with a camera at the distal end of the blade, offering a wide-angle, high-resolution view of the glottic structures. Blades come in many sizes and shapes, accommodating both direct visualization of the glottic structures, as well as indirect (on screen only) views with hyperangulated blades. The on-screen view allows more experienced providers an enhanced degree of oversight during supervision of laryngoscopy.

It is well documented that the use of sedative agents, particularly in combination with neuromuscular blockade (NMB), improves success rates of intubation and decreases associated adverse events. (43)(44)(45)(46) Ozawa et al recently demonstrated that the use of NMB in addition to sedative premedication decreased TIAEs compared with sedative only or no medication groups (10% NMB with sedative versus 29% sedative only and 23% no medication, $P<.001$). (46)

Videolaryngoscopy, the use of NMB to facilitate endotracheal intubation and the use of SADs, particularly as rescue devices in the setting of a failed intubation, are commonplace in the milieu of anesthesiology and may represent an area in which collaboration between specialties could improve patient outcomes.

MULTIDISCIPLINARY HANDOVERS AND NEONATAL PERIOPERATIVE SAFETY

"How do we get to a point of all being on the same page?"

Communication errors are estimated to account for 70% of preventable medical errors, half of which occur during patient handovers. (47) Interdisciplinary, team-based handovers that include all personnel on the current care team (physicians, nurses, respiratory therapists, etc) and an interdisciplinary group of team members receiving patients for a new phase of care can improve the safety, efficiency, and quality of care transitions between intensive care units and operating rooms. (48)(49) Structured handover after cardiac surgery not only reduces loss of information on transfer (43%–16%) but also increases provider satisfaction and leads to earlier postoperative extubation, less cardiopulmonary resuscitation, less mediastinal reexploration, and less severe metabolic acidosis in the first 24 hours after surgery. (50) I-PASS, a structured pediatric handover tool developed and tested as part of a collaboration among a group of pediatric hospitals has been shown to reduce preventable errors by 30% without increasing the duration of oral handovers or computer time. (51) Tables 2 and 3 list details on the elements of the I-PASS acronym and a sample handover discussion. One of the most important aspects of the I-PASS tool is the *synthesis* of information that occurs at the end of the handover by the accepting team.

In many NICUs, perioperative patient handovers do not routinely include the entire surgical and neonatal team, and important aspects of postoperative care can be overlooked. In a recent study that included a Handover Perceptions Survey, 37% of NICU clinicians and 18% of surgical providers had experienced a poor handover that had led to a serious adverse outcome. (52) All perioperative providers who were surveyed expressed a preference for

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TABLE 3. **Example of Verbal Handovers Using the I-PASS Mnemonic**

EXAMPLE OF VERBAL HANDOVER (NEONATOLOGIST TO ANESTHESIOLOGIST BEFORE PDA REPAIR)		
I	Illness severity	This infant is critical and tenuous.
P	Patient summary	The infant is a former 24-week-gestation infant, now 10 days of age, with severe lung disease of prematurity and a large PDA. He was born by emergent cesarean delivery after preterm labor in the setting of severe chorioamnionitis. After birth, he had apnea and bradycardia that responded to intubation, chest compressions, and 1 dose of intravenous epinephrine. His Apgar scores were 1, 1, 6, and 8 at 1, 5, 10, and 15 minutes of age, respectively. He remained intubated since then, requiring progressively higher ventilator settings. He received antibiotics for presumed infection for 1 week. He was noted to have a clinically significant PDA that did not respond to indomethacin courses. He is currently intubated with a 2.5 uncuffed ETT, taped at 7 cm at the lip. He is receiving SIMV with a PIP of 22 mm Hg, PEEP of 6 mm Hg, at a rate of 35, and an Fio$_2$=0.6. His most recent chest radiograph shows severe bilateral hazy lung fields, decreased lung expansion, and an enlarged heart. He is currently NPO and receiving total parenteral nutrition at 130 mL/kg per day through a well-positioned PICC. His laboratory results from yesterday showed normal electrolytes, a hematocrit of 45% and a capillary blood gas of pH 7.28 and a Pco$_2$ 62 mm Hg.
A	Action list	Minimize intravenous fluids given above his maintenance fluid needs and insensible losses.
S	Situation awareness and contingency plan	His ETT was very positional, especially with changes in his head position. It was retaped as best as possible to minimize movement, but if his Fio$_2$ requirement increased and/or worsened and the typical assessments did not yield a cause, the position of his ETT should be evaluated with radiography. Where possible, pressures should be limited during periods of respiratory decompensation.
S	Synthesis by anesthesiologist	This patient is an ex-24-week-gestation infant now with a PMA of 25½ weeks who has severe lung disease of prematurity and is proceeding with a PDA ligation. He had perinatal depression and received antibiotics for 1 week. He is currently receiving high ventilator support and NPO. His fluids and ETT will continue to be monitored while limiting any periods when the ventilator pressures will need to be increased.

EXAMPLE OF VERBAL HANDOVER (ANESTHESIOLOGIST TO NEONATOLOGIST AFTER PDA REPAIR)		
I	**ILLNESS SEVERITY**	**THIS INFANT REMAINS CRITICAL**
P	Patient summary	This is an ex-24-week-gestation infant, now at 25 ½ weeks, PMA, who underwent a surgical PDA ligation under general anesthesia. He was brought to the operating room with a 2.5 uncuffed ETT in situ and, because an intravenous anesthetic was planned, he was able to remain on the NICU ventilator. He received cisatracurium and fentanyl (10 µg/kg total), as well as a dopamine infusion at 5 µg/kg per minute, which is still being infused. Baseline fluids were continued at 130 mL/kg per day with an additional 6 mL of normal saline for flushes and 6 mL of albumin as a 1-time 10 mL/kg fluid bolus for mild hypotension. Beyond a brief desaturation requiring increased minute ventilation during surgical lung manipulation, he tolerated the procedure well.
A	Action list	Anticipate weaning off dopamine once his surgical analgesia wears off, but also continued need for IV analgesics.
S	Situation awareness and contingency plan	His paralytic was re-dosed before transport back to the NICU to maintain maximum control of his airway, so do not expect respiratory effort for at least another hour. Following ligation of his PDA, significant improvement was noted in the lability of his oxygen saturation.
S	Synthesis by neonatologist	This is an ex-24-week-gestation infant, now at 25 ½ weeks' PMA, who has had surgical PDA ligation under general anesthesia. He tolerated the procedure well, and his oxygenation seems less labile. He is currently receiving low-dose dopamine, but this is expected to be weaned as his surgical analgesia wears off.

ETT=endotracheal tube; IV=intravenous; NPO=nil per os (nothing by mouth); PDA=patent ductus arteriosus; PEEP=positive end expiratory pressure; PICC=peripherally inserted central catheter; PIP=positive inspiratory pressure; PMA=postmenstrual age; SIMV=synchronized intermittent mandatory ventilator.

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face-to-face interdisciplinary handovers instead of one-on-one or electronic handovers. However, neonatal and surgical team members expressed different views about who should be present during these face-to-face handovers. (52) A significantly higher percentage of surgical clinicians than neonatal clinicians routinely attended preoperative and postoperative handovers. (52) Moreover, a significantly higher percentage of NICU clinicians reported that direct handovers interfered with other clinical responsibilities and were not satisfied with the timing of these communications. Neonatologists preferred that the handover occur when patients returned to the NICU after a surgical procedure and were more reluctant to be present for preoperative handovers, perceiving preoperative transfers as more disruptive to their daily workflow.

Quality improvement efforts for surgeries in children, including the ACS CSV Quality Improvement Program™ and the Pediatric National Surgical Quality Improvement Program-Pediatric (NSQIP-P), mandate that NICUs that care for surgical patients should designate a surgical director who works in close collaboration with the NICU director to measure neonatal surgical quality and safety and develop perioperative guidelines. As part of these collaborative efforts, several ACS CSV–verified hospitals have developed regular daily meetings among surgeons, anesthesiologists, and NICU staff to discuss all patients scheduled to go to the operating room either that day or the following day to ensure that comprehensive perioperative concerns are discussed by all members of the perioperative care team. Because this meeting is a scheduled event, it allows for structured interdisciplinary communication and feedback. Because of broad agreement among NICU and operating room providers that direct handovers are preferable and likely improve perioperative patient safety, it seems imperative to design and implement a more reliable universal handover process for both preoperative and postoperative face-to-face communication to improve neonatal safety.

SUMMARY

"Hasn't it felt like we've been friends forever?"

- The doubling time for medical knowledge is less than 3 months, leading to ever more specialized medical niches. Unfortunately, one can be fully trained in neonatology without ever receiving formalized training in anesthesiology (and vice versa).
- Although anesthesiologists and neonatologists practice in vastly different circumstances and environments, they are linked by advancements driven by technical innovations.
- Neonates are exquisitely vulnerable to perioperative hypothermia because of heat loss, redistribution, and exposure.
- Neonates can often have profound intraoperative fluid requirements due to significant evaporative losses, translocation, and blood loss.
- The mainstay of neonatal regional anesthesia remains neuraxial blocks: spinal anesthetics, caudals, and epidurals.
- New techniques in regional anesthesia are being used in the neonatal population, such as PV blocks and extremity blocks.
- Chloroprocaine is often the local anesthetic of choice for infusion in neonates because of its metabolism by plasma esterases (not renal or hepatic, which may be immature).
- Anesthesiologists safely use cuffed ETTs intraoperatively in the neonatal population because of concerns about dynamic intraoperative pulmonary mechanics, the need to protect the airway during bowel manipulation, and the knowledge that newer generation cuffed ETTs have minimal circumferential profile when deflated.
- Anesthesiologists routinely use SADs during anesthetic care and as a rescue device during difficult airway scenarios. The use of SADs in the neonatal population as a rescue device is increasing, and consultation with anesthesia regarding best practices is advisable.
- Videolaryngoscopy is another mainstay of pediatric anesthesiology, with its use expanding more to the neonatal population in recent years.
- Structured handovers from service-to-service, such as with the I-PASS method, have been shown to improve patient safety and care.
- Collaborative efforts, such as the ACS CSV Quality Improvement Program™ and the NSQIP-P, represent exciting new avenues for improved patient care and interdisciplinary partnership.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of maternal surgery and anesthesia (eg, appendectomy).
- Know the issues in the organization of perinatal care (e.g., regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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Glucose Homeostasis in Newborns: An Endocrinology Perspective

Emir Tas, MD,* Luigi Garibaldi, MD,† Radhika Muzumdar, MD†

**Division of Endocrinology and Diabetes, Department of Pediatrics, Arkansas Children's Hospital, Little Rock, AR*

†Division of Endocrinology, Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA

Education Gap

Significant advances have been made in our understanding of the hormonal regulation of glucose homeostasis immediately after birth; however, controversies remain over the definition of clinically significant neonatal hypoglycemia, and interpretation of hormone concentrations in asymptomatic neonates with hypoglycemia.

Abstract

Physiologic adaptations in the postnatal period, along with gradual establishment of enteral feeding, help maintain plasma glucose concentrations in the neonatal period. The definition of normal plasma glucose in the neonatal period has been a subject of debate because of a lack of evidence linking a set plasma or blood glucose concentration to clinical symptoms or predictors of short- and long-term outcomes. However, there is consensus that maintaining plasma glucose in the normal range for age is important to prevent immediate and long-term neurodevelopmental consequences of hypoglycemia or hyperglycemia. The specific management strategy for abnormal glucose levels in neonates depends on the underlying etiology, and interventions could include nutritional changes, medications, hormone therapy, or even surgery. Here, we will review the physiological processes that help maintain plasma glucose in newborns and discuss the approach to a newborn with disordered glucose homeostasis, with an emphasis on the endocrine basis of abnormal glucose homeostasis.

Objectives After completing this article, readers should be able to:

1. Describe the physiology of glucose homeostasis in neonates immediately after birth.
2. Recognize that hypoglycemia during the first 24 to 48 hours after birth is nonketotic.

AUTHOR DISCLOSURE Drs Tas, Garibaldi, and Muzumdar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ATP	adenosine triphosphate
CNS	central nervous system
DEND	developmental delay, epilepsy, and neonatal diabetes
FFA	free fatty acid
GCK	glucokinase
GDH	glutamate dehydrogenase
GH	growth hormone
GIR	glucose infusion rate
HI/HA	hyperinsulinism/ hyperammonemia
IGF-1	insulinlike growth factor 1
IGFBP-3	IGF-binding protein 3
IUGR	intrauterine growth restriction
LGA	large for gestational age
NDM	neonatal diabetes mellitus
PES	Pediatric Endocrine Society
PG	plasma glucose
PNDM	permanent neonatal diabetes mellitus
SCHAD	short-chain L-3-hydroxyacyl-CoA dehydrogenase
SGA	small for gestational age
TCA	tricarboxylic acid
TNDM	transient neonatal diabetes mellitus
VLBW	very low birthweight

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3. Appreciate the counterregulatory hormonal responses to declining plasma glucose concentrations in healthy neonates after the transitional period.
4. Explain the steps and the role of the K-ATP channel in insulin secretion.
5. Describe the most common endocrine etiologies of neonatal hypoglycemia.
6. Recognize the risk factors for neonatal hyperglycemia.

INTRODUCTION

The definition of normal plasma glucose in the newborn period has been a subject of ongoing debate (1) because of a lack of evidence linking a set plasma glucose (PG) or blood glucose concentration to clinical symptoms or predictors of short- and long-term outcomes. PG levels are lower in the first 48 hours after birth. In healthy term newborns with no risk factors for hypoglycemia, the PG level correlates positively with postnatal age and birthweight on day 0, (2) and breastfed babies have lower PG concentrations compared with formula-fed babies. (3)(4) Although there is no consensus on the PG concentration cutoffs in the first 2 days after birth among neonatologists and endocrinologists, the Pediatric Endocrine Society (PES) recommends a preprandial cutoff PG concentration of less than 50 mg/dL (2.8 mmol/L) for treatment in all neonates regardless of the presence of risk factors within the first 48 hours. (3) Beyond the transition period of 48 to 72 hours after birth, neonates can maintain PG levels similar to those in older children and adults. (3) Here, we will review the physiological processes that help maintain PG levels in newborns and discuss the treatment approach for a newborn with disordered glucose homeostasis, with an emphasis on the endocrine basis of abnormal glucose homeostasis.

PHYSIOLOGY OF GLUCOSE HOMEOSTASIS IN THE NEWBORN

During pregnancy, the fetus is dependent on the mother for a constant supply of glucose. The relationship between maternal and fetal PG concentrations is linear in mid and late gestation, (5) with minimal difference in their PG levels. However, maternal insulin does not cross the placenta and the fetus makes its own insulin to maintain blood glucose levels. (6) Both in utero and in postnatal life, insulin secretion from the beta cells is tightly linked to PG concentrations. Uptake of glucose into the beta cells via a unique glucose transporter (GLUT2) is the initial step in the insulin secretory process. Once in the cytoplasm, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase (GCK). Further metabolism of glucose through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation results in generation of adenosine triphosphate (ATP). Insulin secretion also occurs in response to other nutrients such as free fatty acids (FFAs) and amino acids. (7)(8) Leucine, alanine, and glutamine can undergo metabolism via α-ketoglutarate and oxaloacetate through the TCA cycle and generate ATP. (9) Increased ratio of ATP to adenosine diphosphate causes closure of K-ATP channels, a type of potassium channel composed of SUR and Kir6.2 subunits, on the beta cell membrane. Closure of K-ATP channels results in depolarization of the beta cell, which then triggers the activation of the voltage-gated calcium channels followed by calcium influx. An increase in the intracellular calcium concentration stimulates insulin release via exocytosis. (10) Metabolic actions of insulin include an increase in cellular glucose uptake, deposition of glucose as glycogen, lipogenesis in adipose tissue, and inhibition of breakdown of triglycerides (lipolysis) and fatty acids (ketone body formation or ketogenesis). Importantly, insulin is also a major fetal growth factor.

With cord clamping at birth, the steady source of glucose from the mother to the infant is abruptly interrupted. In the early hours after birth, until enteral intake is established, the maintenance of PG levels is dependent on the activation of glycogenolysis (breakdown of stored glycogen). Other mechanisms that can provide fuel sources, such as gluconeogenesis (formation of new glucose from noncarbohydrate sources) or ketogenesis, are not established at birth. The levels of glucagon and epinephrine increase after birth, and these hormones mobilize glucose through glycogenolysis. (11) This, along with suppressed insulin levels, maintains lower but stable PG concentrations in the first 4 to 48 hours after birth. In this period, neonates are hypoketotic. (12) Whether the reduced ketogenesis is because of immaturity

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of enzymes, as shown in animal studies, or lower threshold for insulin release in the immediate postnatal period, as demonstrated by studies in isolated islets, remains to be confirmed. (13) Transcription of the gluconeogenic enzymes and ketogenesis are potentially activated 12 to 24 hours after birth in response to fatty acid–rich colostrum and changes in hormonal milieu. (14)

Newborns with low birthweight and intrauterine growth restriction (IUGR) have decreased glycogen stores at birth and, therefore, are at risk for hypoglycemia. (15) These newborns also have low fat stores that further increase their risk for fuel insufficiency. Infants of diabetic mothers, on the other hand, are at risk for hypoglycemia mainly because of the presence of high circulating insulin levels and a delay in glucagon increase. The degree of hyperglycemia and resultant hyperinsulinemia in the fetus are a direct reflection of the metabolic control of diabetes in the pregnant woman, with poorly controlled diabetes resulting in macrosomia. (16) With the establishment of feeding, PG levels gradually increase in most neonates and reach levels found in older children and adults by 48 to 72 hours after birth. (3)

The dynamic interplay between nutrient availability and hormones, such as insulin and other counterregulatory hormones, helps maintain normoglycemia in fed and fasting states. A low PG concentration triggers a complex, well-coordinated, and step-wise neuroendocrine response to counteract hypoglycemia. When the PG concentration drops below 80 to 85 mg/dL (4.4–4.7 mmol/L), still within the physiological range, the first response is to shut off insulin secretion to prevent further decrease in glucose levels. (17)(18) This response also allows the brain to use available glucose in the circulation because glucose can easily pass through the blood-brain barrier in an insulin-independent manner. Furthermore, the decrease in insulin removes the inhibitory effect on lipolysis and ketogenesis, thereby providing alternative fuel sources. (3)(12)(18)

Glucagon, growth hormone (GH), catecholamines, and cortisol are counterregulatory hormones that help mobilize stored glucose and provide alternative fuel sources for energy. Hepatic glycogen serves as the first and immediate source of glucose. With a decrease in PG levels, the increase in glucagon and epinephrine levels promotes hepatic glycogenolysis and provides a source of glucose for a few hours. (19) Epinephrine also inhibits insulin secretion and stimulates glucagon release from the pancreatic islets. Epinephrine and GH promote lipolysis to provide FFAs, which serve as an energy source for skeletal and cardiac muscle. Further β-oxidation of fatty acids (mediated through actions of epinephrine and glucagon) results in the formation of ketone bodies, an alternative energy source for the brain. A continuing decline in glucose concentrations stimulates secretion of other counterregulatory hormones, namely cortisol and GH. Cortisol, along with epinephrine, increases gluconeogenesis from noncarbohydrate sources such as alanine, lactate, and glycerol. Cortisol and GH produce gluconeogenic substrates alanine and glycerol through muscle breakdown and lipolysis, respectively. Also, cortisol increases the transcription of enzymes involved in gluconeogenesis. The purpose of these complex systems is to maintain PG within age-appropriate physiologic ranges and to avoid hypoglycemia-related negative outcomes. The hormonal responses to hypoglycemia are summarized in Fig 1.

Glucose is the primary energy source for the central nervous system (CNS). However, the CNS can use alternative fuel sources, such as ketone bodies and lactate, for a limited duration when glucose is scarce. Because the brain is large compared with the rest of the body in the newborn, the glucose needs of a newborn are significantly higher than those of older children and adults. Newborns need a glucose infusion rate (GIR) of 4 to 6 mg/kg per minute compared with adults who need 1 to 2 mg/kg per minute to maintain PG levels within the normal range. The brains of newborns are also more susceptible to the deleterious effects of low PG levels.

HYPOGLYCEMIA IN THE NEWBORN

Neonates born small or large for gestational age (SGA or LGA), infants of diabetic mothers, and preterm infants are at risk for transient hypoglycemia. Screening for hypoglycemia is the standard of care for these newborns. The incidence of neonatal hypoglycemia during the transition period among at-risk infants varies depending on the cutoff chosen to identify hypoglycemia, the timing of screening in relation to feeding, and the laboratory method used to measure the blood glucose or PG. For instance, Harris et al (4) used a cutoff of less than 47 mg/dL (2.6 mmol/L) and reported an incidence of 51%, whereas Stark et al (20) used a lower cutoff—less than 40 mg/dL (2.2 mmol/L)—and found a 27% incidence in the at-risk group regardless of the age of the infant. The 2015 PES guideline on neonatal hypoglycemia recommends maintaining preprandial PG concentrations above 50 mg/dL (2.8 mmol/L) in the first 48 hours after birth in high-risk neonates without a suspected hypoglycemia disorder. (3) Screening is crucial to identify and treat hypoglycemia promptly, because a growing body of evidence has shown a significant association between neonatal hypoglycemia and long-term negative neurodevelopmental outcomes. (21)(22) McKinlay and

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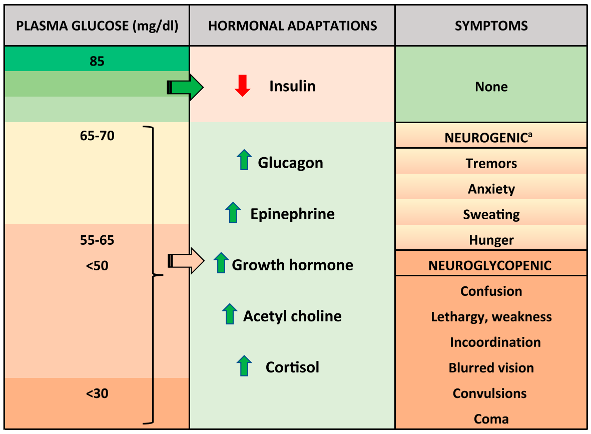

Figure 1. Hormonal responses to hypoglycemia. [a]Symptoms mediated through sympathoadrenal and parasympathetic responses.

colleagues reported a negative association between the duration of blood sugar concentrations outside the arbitrary 54 to 72 mg/dL (3–4 mmol/L) range during the first 48 hours after birth and neurodevelopmental outcomes at 2 years of age. (22) Also, in the same cohort, worse executive and visual-motor integration were noted in children who had more severe and frequent periods of neonatal hypoglycemia at 4.5 years of age. (21)(22)

A healthy newborn is expected to maintain PG concentrations at or above 60 mg/dL (3.3 mmol/L) after 48 hours of age. (3) Although recurrent hypoglycemia is a common metabolic problem in neonates, recognizing neonates at risk for a persistent hypoglycemia disorder is not as straightforward because most neonates are asymptomatic or exhibit nonspecific symptoms. There is no pathognomonic sign or symptom for hypoglycemia. Most of the common symptoms and signs are nonspecific, and include abnormal cry, decreased feeding, jitteriness, irritability, pallor, cyanosis, hypothermia, or diaphoresis. In severe cases, neonates may present with lethargy, tachypnea, hemodynamic instability, apnea, seizures, or even cardiac arrest. (23) A high index of suspicion for a hypoglycemia disorder should be maintained to identify true pathologies and establish appropriate treatment. Though the presence of symptoms or signs of hypoglycemia has been suggested to determine treatment thresholds, current clinical practice is to treat the hypoglycemia without any delay even in the absence of symptoms.

Etiology of Hypoglycemia

A well-coordinated, dynamic balance among intake (feeding), tissue use (glucose uptake, glycolysis, glycogen synthesis), and endogenous production (gluconeogenesis, glycogenolysis) of glucose is necessary to maintain euglycemia. Therefore, a diminished exogenous or endogenous supply, or increased utilization of glucose can cause hypoglycemia. Hypoglycemia can be classified as transient or permanent, but there is no consensus regarding the duration of the hypoglycemia to differentiate one form from the other. Transient hypoglycemia typically resolves within the first few days to weeks.

When hypoglycemia persists beyond the first 48 hours, and hypoglycemia arising from maternal diabetes (the most common type of transient neonatal hypoglycemia) and other common etiologies (SGA, LGA, IUGR) are deemed unlikely, there is a higher risk for permanent pathology. Clinically, permanent hypoglycemia usually has genetic causes. The differential diagnosis of persistent hypoglycemia varies and includes endocrine causes (eg, hyperinsulinemia, GH deficiency, hypocortisolism), as well as nonendocrine causes (eg, inborn errors of metabolism). (24) The causes of neonatal hypoglycemia are listed in Table 1. The timing of hypoglycemia in relation to feedings can provide a clue to the etiology. For instance, postprandial hypoglycemia could be due to dumping syndrome or inborn errors of metabolism, whereas fasting or postabsorptive hypoglycemia is due to hyperinsulinism (HI), defects in glycogenolysis or gluconeogenesis enzymes, or counterregulatory hormonal insufficiency. (24)(25) Because neonates and young infants are fed frequently, hypoglycemia may not occur until after the time between consecutive feedings is spaced out long enough.

Hyperinsulinism. Congenital HI is the most common cause of persistent nonketotic hypoglycemia in the newborn and results from dysregulated insulin secretion. HI could be acquired or inherited, and it can be transient or permanent. Initial biochemical tests cannot distinguish the different forms or types of HI. Demonstrating an elevated insulin concentration along with suppressed plasma ketones and FFAs, and a positive response to a glucagon challenge (ie, an increase in PG concentration over 30 mg/dL [1.6 mmol/L] above baseline) at the time of the hypoglycemia is generally enough to establish the diagnosis of HI. (26)(27) In some cases, the insulin level may be inappropriately normal (instead of low) despite a low PG level; therefore, the term *hyperinsulinism* is preferred over *hyperinsulinemia*. (26)(27) Once the diagnosis of HI is established, a trial of diazoxide, a drug that stabilizes the K-ATP channel in the open state, should be attempted as the first-line medical therapy. The success or failure of the diazoxide trial depends on the extent of preservation of K-ATP channel function. This approach has diagnostic value and may guide future evaluations.

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Stress-induced "transient HI" is an acquired cause of persistent hypoglycemia (despite its name) and is usually associated with birth asphyxia, IUGR/SGA infants, and preeclampsia. (27)(28) The exact pathophysiology is not well understood. It can last several days to weeks after birth; however, some reports show that the course can rarely be prolonged up to a year. (27) Diazoxide is usually effective in the treatment of perinatal stress-induced HI. (29)

The incidence of inherited HI is estimated to be 1 in 50,000 live births; however, it can be diagnosed more often in areas with higher rates of consanguineous marriages. (30) Affected newborns are usually born LGA because of chronic intrauterine exposure to elevated insulin, a fetal growth factor, and present with fasting and postprandial hypoglycemia. (31) HI could be secondary to channelopathies (*ABBC8, KCNJ11*), enzyme anomalies (GCK, glutamate dehydrogenase [GDH], short-chain L-3-hydroxyacyl-CoA dehydrogenase [SCHAD]), or defects in a transcription factor (*HNF4A*). (30) Pathologically, the lesion could be focal or diffuse. Inactivating mutations of the *ABCC8* and *KNCJ11* as the cause of HI are estimated to account for 60% of all identifiable mutations, including the majority (85%) of focal or diffuse diazoxide unresponsive forms. (31)(32) Activating mutations of GCK also result in diazoxide unresponsive HI. (33)

HI resulting from dominant activating mutations of GDH, encoded by *GLUD1*, is a common form of diazoxide-responsive HI. (33) A mild, persistently elevated plasma ammonia level independent of glucose levels is characteristic. This condition is also known as hyperinsulinism/hyperammonemia (HI/HA) syndrome. Leucine, a branch-chained amino acid, directly regulates insulin secretion independent of glucose by allosteric activation of GDH. (34) Affected individuals with HI/HA syndrome have increased sensitivity to leucine-stimulated insulin release. Another rare type of diazoxide-responsive HI occurs because of impaired SCHAD (encoded by *HADH)* activity that leads to disinhibition of GDH. (35) Elevated 3-hydroxybutyryl-carnitine, a metabolite that is routinely screened through the newborn screening programs in some states, is a unique laboratory finding in SCHAD-HI. (33)(36) Ammonia levels are normal in this form. (37) There are a few other but rarer forms of congenital HI, as described elsewhere in the literature. (32)(33)

Hypocortisolism. Adrenal insufficiency, primary or secondary, is a rare cause of persistent neonatal hypoglycemia. Cortisol is one of the key counterregulatory hormones and contributes to glucose homeostasis through enhancement of gluconeogenesis. Cortisol deficiency can lead to hypoglycemia, particularly when enteral feeding is delayed or not adequately established. There is no

TABLE 1. **Etiologies of Neonatal Hypoglycemia**

TRANSIENT	PERSISTENT
Endocrine Causes	

• HI
• Infant of diabetic mother
	• HI
	  • Transient^a (perinatal stress-HI)
	  • Permanent
	    • Channelopathies
	    • Activating GLUD1 mutations
	    • SCHAD deficiency
	    • Other rare genetic HI
	• Panhypopituitarism
	• Isolated GH deficiency
	• Adrenal insufficiency (primary or secondary)

Nonendocrine Causes	

• Delayed enteral feeding
• Prematurity
• IUGR/SGA
• Sepsis
• Maternal use of β-blockers
• Polycythemia
	• Inborn errors of metabolism
	  • Galactosemia
	  • Glycogen storage disease
	  • Gluconeogenic disorders
	  • Fatty acid oxidation disorders
	  • Organic acidurias
	• Hepatic dysfunction

GH=growth hormone; GLUD=glutamate dehydrogenase; HI=hyperinsulinism; IUGR=intrauterine growth restriction; SCHAD=short-chain L-3-hydroxyacyl-CoA dehydrogenase; SGA=small for gestational age.

^{a}Current nomenclature for this type of hypoglycemia, which may, however, last for several weeks or months.

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consensus regarding normal values of cortisol and adrenocorticotropic hormone (ACTH) within the first few weeks of age. Low cortisol levels are often observed in neonates, and are possibly caused by immaturity of the hypothalamus-pituitary-adrenal axis and underdeveloped circadian rhythm. (38) Cortisol deficiency should be suspected as the cause of persistent hypoglycemia in neonates with midline defects such as holoprosencephaly or septo-optic dysplasia. In such circumstances, cortisol deficiency is usually a component of panhypopituitarism. As such, other pituitary hormone concentrations should be assessed, and appropriate treatment should be initiated as applicable. A low cortisol level at the time of hypoglycemia has poor specificity for the diagnosis of adrenal insufficiency. (39) An ACTH stimulation test will help diagnose adrenal insufficiency and distinguish primary versus secondary causes of hypocortisolism.

GH Deficiency. GH is another counterregulatory hormone that is secreted from the anterior pituitary. GH stimulates lipolysis, providing fatty acids and ketone bodies as alternative fuel sources. GH deficiency can be isolated, but it is mostly present as part of panhypopituitarism, especially when the infant is born with a midline defect. GH, cortisol, and thyroxine regulate bilirubin metabolism; therefore, prolonged jaundice, especially when associated with hypoglycemia, may be a sign of panhypopituitarism. (40) A low GH level at the time of hypoglycemia has poor specificity for the diagnosis of GH deficiency in older children. (39) However, GH levels are elevated in neonates regardless of hypoglycemia. Although a low GH level cannot prove deficiency, a random GH concentration of at least 10 to 15 ng/mL (10–15 μg/L) is considered adequate within the first month after birth. (41) Repeated measurements of GH levels should be performed (regardless of the glycemic level) to increase diagnostic value. Provocative tests are rarely indicated in the newborn period. Insulinlike growth factor 1 (IGF1) and IGF-binding protein 3 (IGFBP3) are produced in the liver as a function of GH, and are sensitive markers of circulating GH concentration. The plasma IGF1 level is directly affected by the nutritional status; therefore, it could be falsely low in IUGR/SGA neonates. The plasma IGFBP3 concentration, on the other hand, is more stable and is not affected by the nutritional status. (42) Concomitant measurement of these growth factors may aid in the diagnosis of GH deficiency.

Physical Examination

A thorough physical examination should be performed in all newborns with hypoglycemia regardless of the presence of known risk factors for hypoglycemia. This practice will help guide the diagnostic evaluation, thereby shortening the time to an accurate diagnosis and initiation of appropriate treatment. The diagnosis of LGA may be a sign of exposure to high concentrations of insulin in utero as is the case in infants of diabetic mothers or those born with congenital HI. (43)(44) A diagnosis of SGA may indicate perinatal stress, a well-described condition associated with transient HI. (27) Midline defects or brain malformations (eg, holoprosencephaly) may suggest a pituitary hormone (eg, GH, ACTH) deficiency, either isolated or combined. (45) Infants with hypoglycemia and nystagmus may have septo-optic dysplasia, a well-known midline brain anomaly that is highly associated with hypopituitarism. Presence of syndromic overgrowth conditions (macrocrania and gigantism in Sotos syndrome, hemihypertrophy and macroglossia in Beckwith-Wiedemann syndrome) in a newborn with hypoglycemia may suggest hyperinsulinism. (46)

Laboratory Evaluation

Screening for hypoglycemia is generally done via point-of-care handheld glucometers. These devices use glucose oxidase as a reducing agent and measure capillary blood sugar in a matter of seconds. The capillary blood sugar concentration measured by glucose meters may be 11% lower than the PG level. (47) Therefore, a low glucometer reading should always be verified with PG estimations to avoid misinterpretation of the "critical sample" results. Continuous glucose monitors are widely used in patients with type 1 diabetes, but they have gained attention for use in newborns only recently. They measure glucose concentration in the interstitial fluid, which generally correlates well with PG concentrations; however, hemodynamic instabilities, including thermoregulation problems due to comorbid situations or prematurity, can potentially affect the reliability of the data. Continuous glucose monitoring cannot be a substitute for PG measurements for the diagnosis of hypoglycemia, and currently the evidence to suggest routine clinical use is insufficient. (47)(48)

An infant's history or physical examination findings may guide prioritization of some tests over others, but a considerable percentage of affected neonates usually do not have any identifiable risk factors or physical examination findings. Considering the limitations in daily blood draw volumes and the prevalence of different etiologies, it is reasonable to take a tiered approach (Fig 2). Most endocrinologists recommend obtaining the following blood tests (critical

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sample) as first tier during a confirmed hypoglycemic episode (ie, PG concentration <50 mg/dL [2.8 mmol/L]) to rule out endocrine etiologies: electrolytes, bicarbonate, insulin, β-hydroxybutyrate, FFAs, cortisol, GH, and lactate. A controlled fasting may be needed to induce hypoglycemia if the neonate does not develop hypoglycemia during a frequent feeding schedule. Further evaluation, including measurement of serum amino acid or acyl carnitine profiles, urine organic acid profile, advanced tests for cortisol or GH deficiency, and testing for genetic disorders of hyperinsulinism, will be guided based on clinical course, associated features, and the results of the critical sample (Fig 2). Recent advances in molecular genetics have enabled providers to identify the underlying pathology in the insulin secretory process precisely. Many commercial laboratories offer a congenital HI panel including the most commonly implicated genes: *ABCC8* (SUR1), *KCNJ11* (Kir6.2), *GCK (glucokinase)*, *GLUD1* (GDH), *HADH* (SCHAD), and others. (31)(32)(33)

Management of Hypoglycemia

The goal in the management of neonatal hypoglycemia is to restore PG levels to a safe, age-appropriate range. The symptoms of the affected neonate will determine the route of treatment, enteral versus parenteral, to achieve the desired goal.

Enteral Feeding. Decreased substrate availability, as in the case of delayed enteral feeding, is one of the most common causes for hypoglycemia in all newborns. Enteral feeding should be instituted in all newborns as quickly as possible unless there are contraindications because of other morbidities. Breastfeeding should be encouraged for various health and psychosocial benefits. Breastfed infants were shown to have significantly less recurrent low glucose concentrations compared with formula-fed infants. (23) When hypoglycemia persists on a typical feeding regimen, more frequent feeding regimens or use of calorically dense formulas or fortification of breast milk may be tried.

Recent studies assessed the efficacy of an oral 40% dextrose gel for the treatment or prevention of asymptomatic hypoglycemia in at-risk infants. (49)(50) Harris et al (51) assessed the efficacy of a dextrose gel for the treatment of neonatal hypoglycemia in at-risk neonates. Neonates treated with a dextrose gel (200 mg/kg) had less treatment failure, defined as a blood sugar less than 47 mg/dL (2.6 mmol/L), 30 minutes after the second dose. (51) In addition, the treatment group had less hypoglycemia-related NICU admissions and higher breastfeeding success rates 2 weeks after the hypoglycemia event. (51) Importantly, the groups did not differ with regard to the frequency of neurosensory impairment at the 2-year follow-up. (52) Similar findings of a lack of difference in long-term

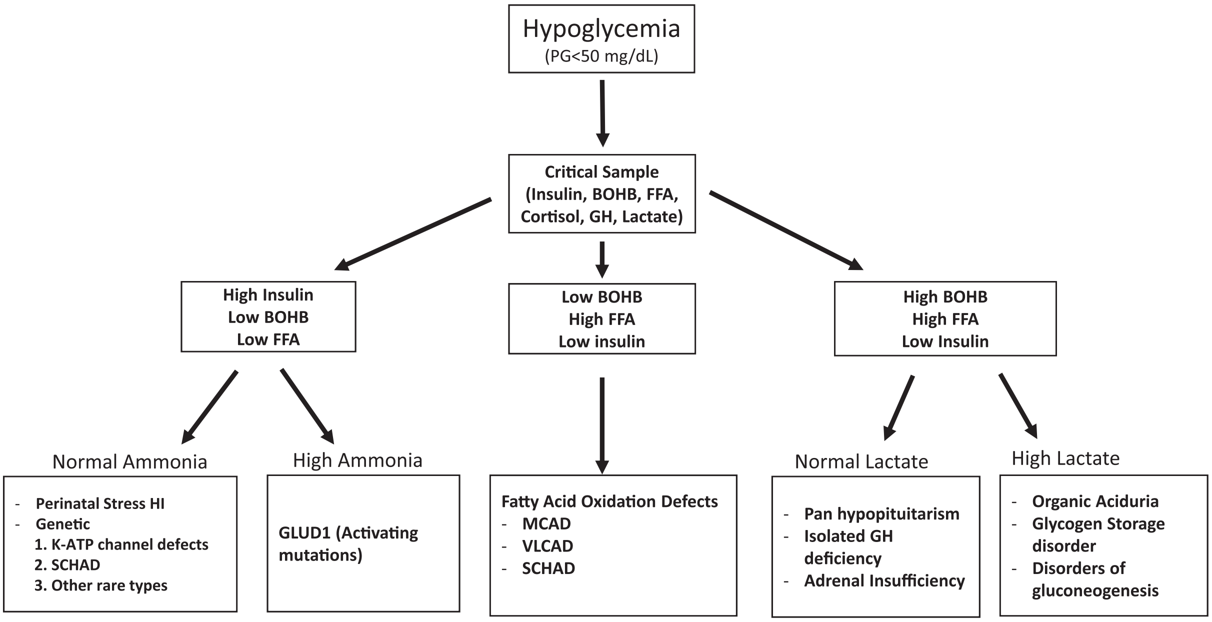

Figure 2. Newborn with persistent hypoglycemia. BOHB=β-hydroxybutyrate; FFA=free fatty acid; GH=growth hormone; GLUD=glutamate dehydrogenase; HI=hyperinsulinism; K-ATP=adenosine triphosphate sensitive potassium channel; MCAD=medium-chain acyl-CoA dehydrogenase; PG=plasma glucose; SCHAD=short-chain L-3-hydroxyacyl-CoA dehydrogenase; VLCAD=very-long-chain acyl-CoA dehydrogenase.

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TABLE 2. **Etiology of Hyperglycemia in Newborn**

Very low birthweight	
Sepsis	
Stress	
Steroid therapy	
Parenteral dextrose	
Neonatal Diabetes	**Other Associated Features**
Transient neonatal diabetes	
6q24 duplication	Intrauterine growth restriction
KCNJ11 mutations	
ABCC8 mutations	
ZFP57	Macroglossia, developmental delay
Permanent neonatal diabetes	
Without exocrine pancreas defects	
KCNJ11 mutations	
ABCC8 mutations	
INS gene mutations	
Glucokinase mutations	
With exocrine pancreas insufficiency	
EIK2AK3	Skeletal dysplasia, liver disease
GATA4, *GATA6* mutations	Cardiac defects
PDX1 mutations	
PTF1A	Neurologic abnormalities, kidney disease
With systemic manifestations	
FOXP3 mutations	Immune dysregulation, dermopathy, enteropathy,
Wolframin mutations	Diabetes insipidus, optic atrophy, deafness, cataracts
KCNJ11	DEND syndrome [developmental delay, epilepsy, neonatal diabetes], neurologic defects
GLIS3	Hypothyroidism, kidney cysts, liver fibrosis, glaucoma
NEUROD1	Learning difficulty, deafness, neurologic deficits
NEUROG3	Diarrhea
HNF1beta	Urogenital defects

neurologic outcomes after the use of a glucose gel were reported at 2-year follow-up by Weston et al. (53) Although a dextrose gel appears to be a promising modality for the treatment of asymptomatic hypoglycemia because of its rapid onset of action, availability, and lower cost, there is no evidence to support its superiority to other nutritional approaches including breast milk or formula feeding in preventing hypoglycemia. Hegarty et al did not find the use of a dextrose gel to be efficacious in preventing neonatal hypoglycemia in at-risk neonates. (54)

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Intravenous Dextrose. When enteral feeding is contraindicated or the newborn suffers from symptomatic hypoglycemia, intravenous dextrose is the treatment of choice for acute management. The standard approach is to give a 2 mL/kg (200 mg/kg) bolus of 10% dextrose followed by a continuous dextrose infusion to achieve euglycemia (55); however, recent evidence recommends caution when using a dextrose bolus for the treatment of asymptomatic hypoglycemia. The main concern with unnecessary bolus treatment is the potential association of rapid correction of hypoglycemia and wide variability in glucose concentrations with negative neurodevelopmental outcomes. (22) Under normal circumstances, a GIR of 4 to 6 mg/kg per minute is usually sufficient in otherwise healthy full-term infants, whereas premature infants may need higher rates, up to 6 to 8 mg/kg per minute, to maintain euglycemia. The GIR should be titrated up to achieve the desired PG range. Infants with hyperinsulinemia usually require higher GIR (>15 mg/kg per min) compared to those without hyperinsulinemia. Placement of a central venous catheter may be needed to deliver high enough glucose concentrations to stabilize PG levels. When dextrose infusion is not enough, or a prolonged and persistent type of etiology is suspected, pharmacologic treatment will be necessary.

Pharmacologic Options. Diazoxide has historically been the first-line treatment for HI and is the only drug approved by the US Food and Drug Administration for the treatment of HI. Diazoxide keeps the beta cell K-ATP channel open, thereby preventing membrane depolarization, a necessary step for normal insulin secretion. Localization of the defect in the insulin secretory pathway and the type of genetic mutation will determine diazoxide responsiveness. For instance, neonates with recessive mutations of *ABCC8* (encoding SUR1 protein) and *KCNJ11* (encoding Kir6.2 protein) are unresponsive to diazoxide whereas infants with activating mutations of GDH or inactivating mutations of SCHAD are responsive to diazoxide. A typical starting dose for diazoxide is 5 to 10 mg/kg per day divided in 3 doses. It may take up to 2 to 3 days until the full therapeutic effect is seen. The dose is usually titrated up gradually until the desired effect is achieved with a maximum dose of 15 to 20 mg/kg per day; however, close monitoring is necessary for a rare but potentially fatal, dose-dependent side effect of fluid retention and pulmonary hypertension at higher doses. (56) Chlorothiazide may be added to the regimen to counteract fluid retention. Hypoalbuminemia was speculated to increase the risk of diazoxide toxicity because this compound is typically bound to plasma proteins at a high percentage. (57) If diazoxide fails to restore euglycemia after a few days of trial, then octreotide, a long-acting somatostatin analog, may be considered because it directly inhibits the opening of voltage-gated calcium channels which are more distal in the insulin secretory pathway. (44)

Octreotide is used as an off-label treatment for diazoxide-unresponsive HI; however, its use has been linked to necrotizing enterocolitis, particularly in preterm infants. (58) It is usually given as a continuous infusion at a dose 5 to 40 μg/kg per day. (59) Tachyphylaxis may develop after a few days of use, even at escalating doses. Safety and efficacy have not been established in the context of HI treatment in neonates; therefore, octreotide should be used with caution, and every effort should be made to shorten the duration of treatment.

Glucagon. Glucagon should be readily available at the bedside of a neonate who is being treated for hypoglycemia with labile control. In addition to its therapeutic effect, glucagon injection also has a diagnostic value. (26) Glucagon can be given in a continuous infusion as a bridge therapy at a dose of 1 mg/day over 24 hours regardless of the birthweight and gestational age of the neonate. (60) Glucagon is generally well-tolerated; however, rebound hypoglycemia, vomiting, hyponatremia, and a rare skin reaction, erythema necrolyticum migrans, have been reported. (61)(62)(63)

Glucocorticoids. Glucocorticoids hypothetically help with the stabilization of blood sugar via enhancement of gluconeogenesis; however, studies have shown that infants treated with hydrocortisone or dexamethasone alone required additional medical treatment to achieve euglycemia. (61)(64)(65) The potential risks associated with the use of glucocorticoid therapy outweigh the benefits, unless the etiology of hypoglycemia is adrenal insufficiency. The use of glucocorticoids for the treatment of persistent hypoglycemia of unknown etiology is not recommended.

Growth Hormone. GH will stabilize PG levels if the etiology of hypoglycemia is GH deficiency. Screening should be undertaken for other pituitary hormones if the neonate is suspected to have hypoglycemia resulting from GH deficiency or adrenal insufficiency. An endocrinology consultation early in the course of management should be considered.

Surgery. Failure of medical intervention to stabilize PG levels warrants exploration of surgery as an alternative treatment for hypoglycemia. Specialized imaging using [^{18}F]fluoro-L-DOPA positron emission tomography with computed tomography distinguishes focal from diffuse lesions in the pancreas and guides surgical intervention. There are currently only 2 congenital HI centers (Congenital Hyperinsulinism Center at the Children's Hospital of Philadelphia, Philadelphia, PA and Cook Children's Hyperinsulinism

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Center, Fort Worth, TX) in the United States where advanced imaging and precision surgery can be performed, including removal of a focal lesion or near total pancreatectomy.

When is a Newborn with a History of Hypoglycemia Safe for Discharge?

The 2015 PES recommendations state that a preprandial PG level of at least 60 mg/dL (3.3 mmol/L) is within the safe range for discharge for most infants; but a concentration of 70 mg/dL or higher (≥3.9 mmol/L) is recommended if a persistent hypoglycemia disorder is suspected, or if the infant is receiving pharmacologic treatment for hypoglycemia. (3) A safety fast should always be done to determine whether the neonate could be safely discharged from the hospital. Duration of a safety fast is typically 6 to 8 hours in the first month after birth, which can be conducted by skipping a mealtime feeding while closely monitoring the blood sugar until the test is complete. The infant's blood sugar level should remain above 60 mg/dL ([3.3 mmol/L] or 70 mg/dL [3.9 mmol/L] if any medication treatment has begun or the patient is suspected to have hypoglycemia with a permanent etiology) before the infant is considered safe to be discharged.

HYPERGLYCEMIA

In a term newborn, hyperglycemia is a much less common clinical problem than hypoglycemia. However, it is a common metabolic abnormality in low-birthweight, preterm, and critically ill newborns. (23) The definition of hyperglycemia in newborns varies, with the most accepted being any PG concentration greater than 125 mg/dL (6.9 mmol/L). However, studies examining consequences of hyperglycemia or treatment thresholds have used varying and higher glucose thresholds. For instance, Zamir et al set levels more than 180 mg/dL (10 mmol/L) as the threshold for hyperglycemia when evaluating consequences, and Lemelman et al recommend treatment with insulin if glucose levels are above 250 mg/dL (13.8 mmol/L). (66)(67)

It is important to recognize and manage hyperglycemia in newborns as it could have significant consequences. Immediate consequences include dehydration, ketosis, diabetic ketoacidosis, poor growth, weight loss, poor perfusion, and susceptibility to infection; (23) long-term consequences include negative effects on neurodevelopmental outcomes. (68)(69) Changes in osmolality and blood flow, endothelial injury, intracellular acidosis, and increased oxidative stress have been implicated in hyperglycemia-mediated injury and its consequences. (70)

Etiology of Hyperglycemia

Risk factors for hyperglycemia in preterm and very-low-birthweight (VLBW) infants include critical illness, infection, stress, medications, parenteral glucose administration, and inadequate pancreatic insulin production. (71) Infections, sepsis, and stress lead to release of cytokines and stress hormones that decrease peripheral glucose utilization as well as increase gluconeogenesis, thereby contributing to hyperglycemia. (23)(70) When glucose levels are persistently greater than 250 mg/dL (13.8 mmol/L) in the absence of identifiable causes, and persist beyond 7 to 10 days of age, neonatal diabetes mellitus (NDM) should be considered. (66)

NDM is rare and estimated to affect 1 in 90,000 to 160,000 live births. (66) By definition, NDM is diabetes diagnosed by 12 months of age, though most infants are diagnosed by 6 months of age. It can result from a range of defects in the beta cells that affect normal development, glucose sensing, metabolism, insulin synthesis, insulin secretion, or enhance beta cell apoptosis. The etiology of NDM is most often monogenic, especially in term infants. Preterm infants could also have a monogenic etiology for their diabetes (31% of cases) and tend to present at an earlier age than full-term infants. (72) NDM could be transient (TNDM) or permanent (PNDM).

Infants with TNDM present earlier on average compared with infants with the permanent form of NDM and outgrow their need for insulin by 3 to 18 months of age. (73) Diabetes may recur at puberty, pregnancy, or in older age, and in some cases, permanent diabetes mellitus may result. The most common cause of TNDM (70%) is related to the 6q24 region of the chromosome. Normally, 6q24 is only paternally expressed. TNDM occurs when 2 copies of this region are expressed due to uniparental disomy, duplication of the paternal allele, or lack of suppression of expression of maternal allele. Other reported features include IUGR, umbilical hernia, macroglossia, deafness, hypotonia, and developmental disabilities. The second most common cause of TNDM (25%) is heterozygous mutations in *ABCC8* or *KCNJ11* (both genes are located in chromosome 11p15.1). Rare causes of TNDM include homozygous or compound heterozygous mutations in transcription factor Zinc Finger protein 57 (gene located in chromosome 6p22.1).

The most common defects leading to PNDM were found in *KCNJ11* and *ABCC8,* genes that encode subunits of the K-ATP channel in the beta cell, accounting for 45% of cases when there is parental consanguinity. (74)(75)(76)(77) KCNJ11 channels are also found in the brain, and therefore children with mutations in *KCNJ11* may have other

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neurologic features such as developmental delay, epilepsy, and neonatal diabetes (DEND syndrome). Indeed, neurologic features are the most common extrapancreatic feature in infants with NDM. (74) Insulin gene mutations (*INS1*) account for 10% to 15% of PNDM cases, (78) and do not differ in incidence based on parental consanguinity. (74) Defects in GLUT2 or GCK, leading to impaired or absent sensing of glucose by the beta cell, and mutations of voltage-gated calcium channels can also result in NDM. (79)(80)(81)

Other genes implicated in NDM include genes involved in beta cell health, immunity, and pancreatic development. Beta cell destruction is associated with mutations in *INS, EIF2AK3* (Wolcott-Rallison syndrome), *IER3IP1, FOXP3* (IPEX syndrome), and *WFS1* (Wolfram syndrome). (66) In these instances, the presence of other clinical features points to specific etiologies, though some associated features may appear much later. Specifically, *FOXP3* defects present with immune dysregulation, skin rash, and diarrhea, many of which may be noted later in life. (82) Defects in *WFS-1* (Wolfram syndrome) should be considered in an infant with diabetes, deafness, and ocular manifestations, though diabetes is usually a later presentation. Generalized defects in the genes involved in pancreatic development such as *PDX1 (IPF1), PTF1A, HNF1B, RFX6, GATA4, GATA6, GLIS3, NEUROG3, NEUROD1, PAX6, NKX2-2,* and *MNX1* can result in exocrine pancreatic insufficiency and neonatal diabetes. (66)

The etiology of hyperglycemia in the newborn is summarized in Table 2.

Diagnosis of Hyperglycemia

Hyperglycemia in the neonate can be insidious and only detected on routine laboratory tests or urinalysis. Infants are at risk for dehydration, acidosis, failure to thrive, and poor weight gain. Symptoms and signs such as tachypnea and desaturations may be seen if there is progression to diabetic ketoacidosis. Rarely, features of altered sensorium or stroke can be seen in response to hyperviscosity and severe hyperglycemia.

The possibility of an infection should be considered in neonates with hyperglycemia, especially preterm and VLBW infants, because hyperglycemia may be a presenting sign of an infection or sepsis. A thorough family history should be elicited in newborns with hyperglycemia and suspected NDM, because the genetic mutations that lead to NDM may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. IUGR and low birthweight are noted in NDM associated with *KCNJ11, ABCC8, 6q24, INS,* and *GCK* mutations.

The physical examination can offer clues to the etiology of diabetes, though some of the features of syndromic diabetes may not become clinically evident until later. In the context of neonatal hyperglycemia, presence of macroglossia and umbilical hernia suggest 6q24-related TNDM; the presence of cardiac defects may point to mutations in *GATA6* or *GATA4*; and the presence of diarrhea may point to exocrine pancreatic insufficiency and mutations in *NeuroG3* or *FOXP3*. Neurologic manifestations may occur in NDM of many genetic etiologies including *KCNJ11* mutations. The finding of skeletal dysplasia along with NDM suggests Wolcott-Rallison syndrome. (83) For a more detailed list of etiologies, we refer the reader to the review on NDM by Lemelman et al. (66)

Management of Hyperglycemia

The initial management of hyperglycemia should include decreasing intravenous dextrose concentrations, correction of dehydration, addressing the underlying conditions that could contribute to stress (eg, hypoxia, acidosis, poor perfusion, infections), and if possible, stopping medications such as steroids or catecholamines that could contribute to hyperglycemia. Increasing the rate of the amino acid infusion could increase protein synthesis, anabolism, and insulin secretion, thereby reducing hyperglycemia. Establishing enteral feedings to augment gut-derived hormones (incretins) and decreasing lipid infusion rates to decrease gluconeogenesis and insulin resistance have also been shown to help correct hyperglycemia. (23)(84)

Hyperglycemia may persist in spite of all the aforementioned interventions, and some preterm neonates may need short-term insulin therapy. Zamir et al reported a lower mortality in extremely preterm infants with hyperglycemia who were treated with insulin (67); however, larger, controlled, prospective studies are needed to validate these observations. Care should be given to prevent hypoglycemia with insulin therapy, because hypoglycemia as well as glucose variability can affect outcomes. (85)

When a diagnosis of NDM is suspected, ultrasonography of the pancreas should be performed to look for developmental defects. Genetic testing for NDM should be performed to confirm the diagnosis and establish the etiology, because therapies vary based on underlying cause. In infants diagnosed with NDM, insulin or sulfonylureas are the main lines of therapy. Mutations in K-ATP channel (*KCNJ11* and *ABCC8* mutations) may respond to sulfonylureas. A trial of sulfonylurea in consultation with endocrinology may be warranted in neonates with NDM even before the genetic diagnosis is confirmed. (86)(87)(88)

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Sulfonylurea treatment may ameliorate neurologic outcomes in DEND syndrome. (88)(89) Families with an infant with IPEX syndrome may need counseling, and early stem cell transplantation could be beneficial in these cases. (82)

SUMMARY

Concentrations of PG in the newborn period are maintained in the normal range for age through postnatal adaptations and gradual establishment of enteral feeding. In the event of hypoglycemia, a concerted counterregulatory mechanism coordinates various physiological processes to provide glucose or alternative fuel sources such as ketone bodies, especially to the brain. Maintenance of PG in the normal range is important to prevent immediate and long-term consequences of hypoglycemia or hyperglycemia on neurodevelopment. The specific management strategy for abnormal glucose levels depends on the underlying etiology, and interventions could include nutritional changes, medications, hormone therapy, or even surgery.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the amino acid substrates for gluconeogenesis.
- Know the fuels used for brain metabolism.
- Know the relationship of maternal blood glucose to fetal glucose uptake and metabolism.
- Know the normal range of endogenous glucose production in term and preterm infants.
- Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes.
- Recognize the clinical and laboratory features of neonatal hypoglycemia.
- Recognize the approach to therapy and prevention of neonatal hypoglycemia.
- Know the potential sequelae of neonatal hypoglycemia.
- Know the causes, including genetic disorders and other clinical conditions, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the clinical and laboratory features and approach to therapy of neonatal hyperglycemia, including transient diabetes mellitus.

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1. Hypoglycemia is a common problem in the newborn period. With the abrupt interruption of the constant transplacental supply of glucose, rapid metabolic adaptation must occur to maintain stable plasma glucose levels postnatally. Subsequently, the maintenance of normoglycemia requires a dynamic balance between nutrient intake and hormones. Which of the following statements regarding postnatal metabolic adaptation is correct?
   A. Gluconeogenesis is an important mechanism of glucose metabolism immediately after birth.
   B. Cortisol decreases the transcription of enzymes involved in glycogenolysis.
   C. The levels of glucagon and epinephrine increase after birth, and these hormones mobilize glucose through glycogenolysis.
   D. Growth hormone inhibits lipolysis.
   E. Beta oxidation of free fatty acid does not occur during the neonatal period.
2. Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in the newborn period. HI can be transient or permanent. Which of the following statements regarding HI is correct?
   A. HI is characterized by elevated insulin concentration, plasma ketones, and free fatty acids.
   B. Neonates with HI have a positive response to a glucagon challenge.
   C. Neonates with HI are typically small for gestational age.
   D. Transient HI secondary to stress is not typically responsive to diazoxide.
   E. The most common cause of inherited HI is growth hormone deficiency due to panhypopituitarism.
3. Laboratory evaluations are necessary to establish the etiology of persistent hypoglycemia in the neonate. First-tier laboratory evaluation, the so-called critical sample, includes the measurement of insulin, β-hydroxybutyrate, free fatty acid, cortisol, growth hormone and lactate levels at time of confirmed hypoglycemia (< 50 mg/dL). Which of the following statements regarding the laboratory evaluation of persistent hypoglycemia in the neonatal period is correct?
   A. Capillary blood sugar measured by glucose meter has been shown to be about 10% higher than plasma glucose levels.
   B. High insulin level during critical laboratory evaluation is most indicative of either panhypopituitarism or isolated growth hormone deficiency.
   C. A high free fatty acid level is pathognomonic for a fatty acid oxidation defect.
   D. High insulin levels along with absent ketones point toward HI.
   E. High lactate levels in the setting of hypoglycemia and low insulin levels are suggestive of adrenal insufficiency.
4. Transient hyperglycemia is a common problem in low-birthweight, preterm, and critically ill neonates. In contrast, neonatal diabetes mellitus (NDM) is rare and is, by definition, diagnosed before age 12 months. NDM should be suspected in neonates with hyperglycemia greater than 250 mg/dL (13.8 mmol/L) and persisting for more than 7 to 10 days after birth. Which of the following statements regarding NDM is correct?
   A. Infants with transient NDM present earlier than those with permanent NDM.
   B. Infants with transient NDM typically outgrow their need for insulin by 18 to 24 months of age.
   C. Most cases of transient NDM are due to maternal uniparental disomy in chromosomal region 6q24.
   D. Insulin gene mutations are a common cause of permanent NDM when there is a history of parental consanguinity.
   E. DEND (developmental delay, epilepsy, neonatal diabetes) syndrome is caused by a mutation in *ABCC8*.

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5. Hyperglycemia in neonates can be insidious and only detected on routine laboratory tests or urinalysis. Neonates with hyperglycemia are at risk for dehydration, acidosis, failure to thrive, and poor weight gain, as well as adverse neurodevelopmental outcomes. Which of the following mechanisms has not been implicated in hyperglycemia-mediated adverse consequences?
   - A. Increased plasma osmolality.
   - B. Endothelial injury.
   - C. Dehydration
   - D. Increased oxidative stress.
   - E. Intracellular alkalosis.

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Thyroid Function During the Fetal and Neonatal Periods

Liane Eng, MD,* Leslie Lam, MD*

**Division of Pediatric Endocrinology and Diabetes, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY*

Education Gaps

1. Interpretation of thyroid function tests for newborns in the NICU can be challenging.
2. An understanding of the normal development of the thyroid gland and the hypothalamic-pituitary-thyroid axis can enable physicians to better interpret the thyroid function tests for neonates, especially those in the NICU.

Abstract

Thyroid hormones are essential during infancy and childhood for growth and brain development. The formation and maturation of the newborn's hypothalamic-pituitary-thyroid axis begin in utero with fetal dependence on maternal thyroid hormones early in the pregnancy. As the fetal thyroid gland begins to produce thyroid hormones in the second trimester, the reliance decreases and remains at lower levels until birth. After birth, the detachment from the placenta and the change in thermal environment lead to a rapid increase in circulating thyroid-stimulating hormone in the neonate within hours, resulting in subsequent increases in thyroxine and triiodothyronine concentrations. Preterm infants may have lower thyroxine concentrations because of an immature hypothalamic-pituitary-thyroid axis at the time of birth and premature discontinuation of transference of maternal thyroid hormones. Similarly, infants with critical illness unrelated to the thyroid gland may have lower thyroxine levels. Infants born to mothers with Graves' disease are at risk for hypothyroidism and hyperthyroidism, which is related to the placental transfer of maternal autoantibodies, as well as antithyroid medications. An understanding of the normal embryology and physiology of the fetal and neonatal thyroid will help in evaluating a newborn for thyroid disorders.

Objectives

After completing this article, readers should be able to:

1. Explain the timing of fetal thyroid gland development and maturation of the hypothalamic-pituitary-thyroid axis.

AUTHOR DISCLOSURE Drs Eng and Lam have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

HPT	hypothalamic-pituitary-thyroid
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroxine-binding globulin
TRAbs	thyroid-stimulating hormone receptor antibodies
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone

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2. Describe the role of maternal thyroid hormones in fetal thyroid development.
3. Describe the changes in thyroid hormone production in the newborn immediately after birth.
4. Explain how the newborn's health status affects thyroid function.

INTRODUCTION

Adequate maternal levels of thyroid hormones are critical for fetal and neonatal growth and brain development. Insufficient maternal levels during pregnancy are associated with cognitive impairment in the child later in life. (1)(2) Early detection and treatment of hypothyroidism in the pregnant woman and in the neonate after birth reduce the risk for developmental delays and have led to the inclusion of congenital hypothyroidism in universal newborn screening programs throughout the United States. A basic understanding of the embryology of the thyroid gland and the genesis of the hypothalamic-pituitary-thyroid (HPT) axis is necessary when evaluating a newborn for possible thyroid disorders. This review provides a general overview of fetal thyroid development and fetal and neonatal thyroid physiology.

FETAL THYROID GLAND DEVELOPMENT

The thyroid gland originates from the endoderm and is identifiable by the fourth week of gestation. (3) It is mainly derived from the median anlagen (thyroid diverticulum) located in the primitive pharyngeal floor, which gives rise to the follicular cells. There is also a contribution from the lateral anlagen of the fourth pharyngeal pouches, which later form the calcitonin-secreting parafollicular cells. (4) The median anlagen begins its descent along the thyroglossal duct on days 16 to 17 of gestation, and fuses with the lateral anlagen in the anterior neck to form the thyroid gland by day 50 of gestation. (3) The thyroglossal duct subsequently regresses, leaving the foramen cecum as the only remnant of this embryologic structure.

FETAL THYROID HORMONE PRODUCTION AND MATERNAL THYROID INFLUENCE

Thyroid hormones are essential during pregnancy for fetal development, in particular, fetal neurogenesis. (5) Fetal thyroid hormone production remains low in the beginning of pregnancy and rises to significant levels starting in the second trimester (Fig). This delay in fetal production is related to the time needed for the thyroid gland and HPT axis to mature in utero. The fetal hypothalamus begins secreting thyrotropin-releasing hormone (TRH) around the eighth week of gestation, which stimulates the fetal pituitary gland to secrete thyroid-stimulating hormone

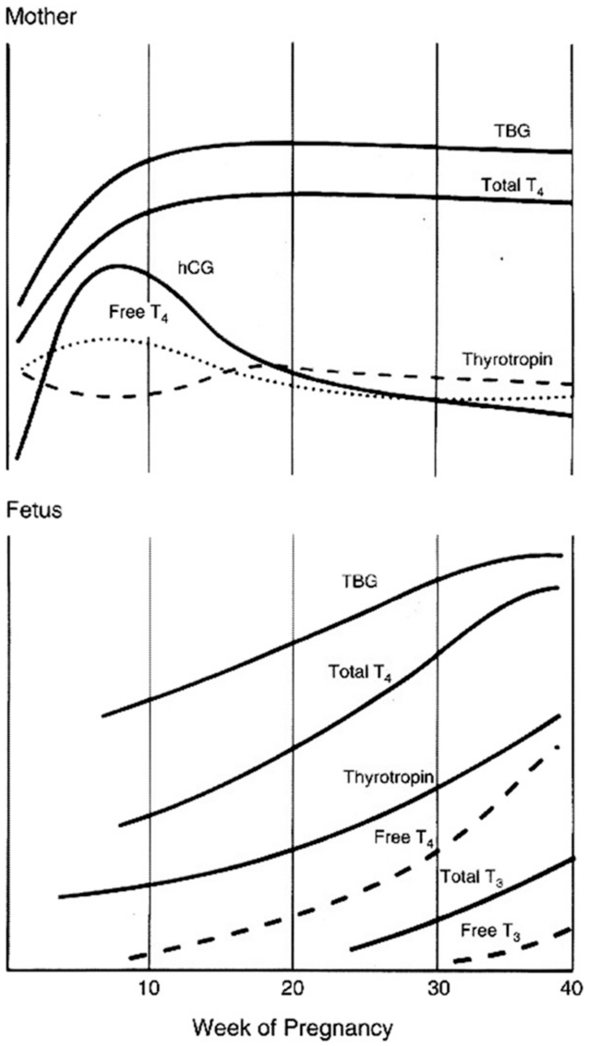

Figure. Relative changes in maternal and fetal thyroid function during pregnancy. hCG=human chorionic gonadotropin; TBG=thyroxine-binding globulin; T_4=thyroxine; Thyrotropin=thyroid-stimulating hormone; T_3=triiodothyronine. Reprinted with permission from Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *N Engl J Med.* 1994;331(16):1072–1078. (9)

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(TSH). (6) Despite the high concentration of TRH, the TSH concentration in the fetal circulation remains low until 18 to 20 weeks of gestation when the thyroid gland functionally matures, after which it increases gradually to a peak of 6 to 8 μU/mL (6–8 mU/L) by term gestation. (7) In response to the increasing TSH concentration, thyroxine (T_4) level increases. Circulating triiodothyronine (T_3), the active thyroid hormone derived from deiodination of T_4 at target tissues, is low until the 30th week of gestation. (6) The rising T_4 level has minimal inhibition on TSH secretion in utero because of the immaturity of the negative feedback response in the fetal pituitary gland. In fact, the HPT axis does not become fully functional until about 1 to 2 months after birth. (8)(9)

The thyroid hormones T_4 and T_3 are important for fetal growth and development, yet the fetal thyroid gland does not produce appreciable quantities of either until the second trimester. The fetus is, therefore, dependent on maternal contribution as the major source of thyroid hormone during pregnancy, especially during the first trimester. Indeed, the fetal T_4 level during the first trimester is reflective of maternal thyroid hormone levels. This dependence decreases as the fetal thyroid hormone production increases and the HPT axis matures. Even so, at birth, maternal T_4 comprises 30% to 50% of T_4 measured in cord blood, demonstrating the continued dependence of the fetus on maternal thyroid hormones until delivery. (10)

An euthyroid state in the pregnant woman is important not only for fetal life but also for the neurodevelopment of the child postnatally. Several studies have shown that children born to mothers with low T_4 levels during pregnancy have lower IQs than children born to mothers with normal T_4 concentrations. (1)(2) In addition, these children may have expressive language and nonverbal delays. (11)(12) Maternal hypothyroidism, particularly during the first trimester, has been associated with delayed neurodevelopment in the child. (2)(13) In response to the fetal reliance on maternal thyroid hormones, the mother's T_4 concentration increases by 20% to 50% during pregnancy. (14) This is accompanied by increased availability of thyroxine-binding globulin (TBG) and requires adequate iodine intake by the pregnant woman. Adequate maternal iodine stores are paramount to fetal thyroid growth because the fetus relies entirely on the mother as an iodine source for thyroid hormone production. Iodine deficiency during pregnancy can lead to severe hypothyroidism and cretinism. The incidence of hypothyroidism has decreased in developed countries since the addition of iodine in common ingredients such as table salt but remains a concern in developing countries. For women who are diagnosed with hypothyroidism before or during pregnancy, initiation of levothyroxine replacement with subsequent normalization of T_4 levels prior to the third trimester is associated with normal intellectual outcomes in the offspring. (15)(16) Guidelines for the management of thyroid dysfunction during pregnancy were published by the Endocrine Society in 2012 and the American Thyroid Association in 2017. (17)(18)

TRH and T_4 readily cross the placenta from the pregnant woman to the fetus, allowing for growth and maturation of the thyroid gland and HPT axis. However, substances that negatively affect fetal thyroid development can also traverse the placenta if present in the pregnant woman, including thyroid autoantibodies and antithyroid medications. Maternal TSH receptor antibodies (TRAbs), which can be stimulating or inhibiting, cross the placenta, bind to thyroid follicular cells, and alter fetal thyroid hormone production, leading to transient neonatal hyperthyroidism or hypothyroidism, respectively. (19) Neonatal Graves' disease is briefly discussed in a later section.

TRANSITION FROM FETAL TO NEONATAL THYROID HORMONE PRODUCTION

At birth, several changes occur that stimulate neonatal thyroid hormone production. First, the infant has to make a transition from the warm uterine environment to the cool extrauterine setting. This promotes the neonatal hypothalamus to secrete TRH, which stimulates the pituitary gland to actively secrete TSH, leading to a TSH surge. TSH rises to a peak of 60 to 80 μU/mL (60–80 mU/L) by 30 minutes after birth, then decreases to normal term infant levels by 3 to 5 days of age. (4)(20) The TSH surge stimulates the neonatal thyroid to produce T_4, whose concentration peaks by 48 hours after birth with maximum total T_4 and free T_4 of 209 nmol/L (16 μg/dL) and 90 pmol/L (7 ng/dL), respectively. (21) As opposed to the TSH level, which normalizes within days, normalization of T_4 levels may require several weeks. (22) T_3 production in the neonate also increases, rising by fourfold within the first few hours after birth. (8)(23)

NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

Early detection and treatment of hypothyroidism in the neonate improves brain function and limits the cognitive impairment of the affected child. This observation, made during the middle of the 20th century, led to the implementation of universal newborn screening for congenital hypothyroidism in all 50 states by the 1970s and publication

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of recommended guidelines. (24) Newborn screening is ideally performed on the 2nd to 4th day after birth in term newborns and within the first 7 days after birth in preterm neonates. (25) Most states use TSH for primary screening, with T_4 as second-tier testing. Testing before the recommended time may be detecting the physiologic TSH surge, leading to falsely abnormal results. The use of TSH for primary screening may also fail to detect TBG deficiency and central hypothyroidism. Other states use T_4 as the first-tier screening, with reflex TSH testing for borderline or abnormal results. This method of screening, however, may miss primary hypothyroidism presenting as delayed TSH elevation. This can be prevented by requiring a repeat second TSH test 2 to 4 weeks after the initial results. Updated guidelines by the American Academy of Pediatrics for screening and management of congenital hypothyroidism were published in 2006. (25)

DIFFERENCES IN THYROID FUNCTION TEST PATTERNS BASED ON NEONATAL STATUS

Prematurity

Neonates born preterm, particularly before 34 weeks of gestation, have lower T_4 concentrations compared with infants born at term. (7) This is a consequence of the premature, abrupt discontinuation of maternal thyroid hormone transfer through the placenta. In addition, the immaturity of the HPT axis in preterm infants leads to an attenuated (or absent) increase in T_4 in response to the TSH surge after birth. The combined effect leads to lower total T_4 and free T_4 levels in preterm infants, referred to as *hypothyroxinemia of prematurity*. (26)(27) This benign biochemical finding tends to be a transient condition that gradually resolves as the infant's HPT axis matures, which often takes several weeks beyond term corrected gestational age.

Nonthyroidal Critical Illness

Newborns with nonthyroidal critical illness, such as bacteremia, lung disease, or necrotizing enterocolitis, most often have a sick euthyroid picture characterized by low T_4 and T_3 levels. T_3 is typically more affected because of the inhibition of the enzymes that convert T_4 to T_3. (28) The T_4 concentration is inversely related to the severity of the illness. (6) The risk of mortality is highest in infants with low T_3 and concomitantly low T_4 and TSH levels. (29)

Neonatal Graves' Disease

Neonates born to mothers with Graves' disease, either diagnosed during pregnancy or poorly controlled during pregnancy, are exposed in utero to high T_4 and T_3 concentrations. In addition, stimulating TRAbs freely cross the placenta, activate the TSH receptors, and upregulate fetal thyroid hormone production. This leads to complications during pregnancy, including gestational hypertension, preeclampsia, intrauterine growth restriction, and preterm birth. Postnatally, the infant is at risk for neonatal hyperthyroidism, characterized by high T_4 and T_3 levels with concomitant low or suppressed TSH concentrations. Management guidelines of infants born to mothers with hyperthyroidism were recently published. (19)

Newborns of mothers with Graves' disease can also develop hypothyroidism, either transient or permanent. Transient hypothyroidism may occur because of several factors, including the presence of inhibiting TRAbs and antithyroid medications that cross the placenta. (16)(30)(31)

CONCLUSION

Development of the fetal thyroid gland and maturation of the HPT axis is a complex process that relies heavily on maternal thyroid hormones and iodine stores during pregnancy, particularly in the first trimester. Familiarity with the physiology of thyroid hormone production during the fetal and neonatal periods is important when evaluating a newborn for thyroid disorders.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the relationship between fetal and maternal thyroid physiology.
- Know the embryology and normal physiological function of the thyroid gland.
- Know the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction.

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NeoReviews Quiz

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1. Thyroid hormones play a critical role in fetal development. Which of the following statements regarding thyroid hormones during pregnancy is correct?
   - A. Fetal thyroid hormone production typically begins at the 30th week of gestation.
   - B. Thyrotropin-releasing hormone (TRH) is not produced by the fetus and therefore, the fetus depends on maternal signaling to initiate thyroid-stimulating hormone (TSH).
   - C. TSH concentration in fetal circulation remains low until 18 to 20 weeks of gestation when the thyroid gland functionally matures.
   - D. During the fetal period, free triiodothyronine (T_3) levels are always higher than free thyroxine (T_4) levels.
   - E. Both T_4 and T_3 exert a strong inhibitory signal on TSH secretion in utero because of a hyperresponsive negative feedback response in the fetus.
2. Because of relatively low thyroid hormone production by the fetus, maternal contribution of thyroid hormone plays an important role in development. For infants born at term, what percentage of the T_4 measured in cord blood consists of maternal T_4?
   - A. Zero.
   - B. 10%.
   - C. 30%–40%.
   - D. 50%–60%.
   - E. 90%.
3. A pregnant woman presents during her third trimester with a history of hypothyroidism and inconsistent adherence to thyroid hormone replacement therapy. Which of the following statements regarding hypothyroidism during pregnancy is correct?
   - A. Children born to mothers with low T_4 levels during pregnancy have lower IQs than children born to mothers with normal T_4 concentrations.
   - B. Maternal hypothyroidism during the third trimester, more so than earlier during pregnancy, appears to confer the highest risk for delayed neurodevelopment in the child.
   - C. T_4, but not TRH, crosses the placenta from the pregnant woman to her fetus.
   - D. To supply fetal development, the pregnant woman's T_4 concentration increases by 100% to 200% during pregnancy.
   - E. The mainstay of treatment for maternal hypothyroidism in developed countries is iodine supplementation, as levothyroxine is contraindicated during pregnancy because of its teratogenic effects.
4. A term newborn receives routine newborn screening, which includes screening for congenital hypothyroidism. Which of the following statements about screening is correct?
   - A. Because it is not an established benefit, screening for hypothyroidism in 2019 occurred in only 25 states.
   - B. Newborn screening is ideally performed on the second to fourth day after birth in term neonates and within the first 7 days after birth in preterm neonates.
   - C. Using TSH level as the primary screening test is the most sensitive method for thyroxine-binding globulin deficiency and central hypothyroidism.
   - D. Using T_4 as first-tier screening will be close to 100% sensitive for primary hypothyroidism presenting as delayed TSH elevation.
   - E. Most states use both TSH and T_4 as the first-line screening test.

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5. A female infant born at 26 weeks of gestation is being cared for in the NICU and is now 3 weeks old. She had respiratory distress syndrome, treated with nasal continuous positive airway pressure for the first week after delivery, and is now breathing room air. Thyroid function testing is performed as part of usual screening. Which of the following statements about preterm infants and thyroid function testing is correct?

   A. Neonates born preterm have lower TSH, but equal T_4 concentrations compared with infants born at term.
   B. Thyroid function testing in preterm infants should be delayed until 40 weeks' gestational age, because it is not useful to test thyroid function earlier, as results are often misleading and uninterpretable.
   C. Hypothyroxinemia of prematurity is increasingly recognized as a pathologic condition that is permanent and leads to severe neurodevelopmental delay.
   D. The immaturity of the hypothalamic-pituitary-thyroid axis leads to an attenuated or absent increase in T_4 in response to the TSH surge after birth.
   E. While thyroid hormone and associated levels are often different for preterm infants compared with established term infant values during the first 1 or 2 days after delivery, these levels should normalize to those of term infants by 3 to 4 days of age.

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Thyroid Function During the Fetal and Neonatal Periods

Liane Eng and Leslie Lam

NeoReviews 2020;21;e30
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The Laboratory Features of Congenital Hypothyroidism and Approach to Therapy

Alyson Weiner, MD,* Sharon Oberfield, MD,* Patricia Vuguin, MD*

*Department of Pediatric Endocrinology, Columbia University Medical Center, New York, NY

Practice Gaps

1. Congenital hypothyroidism is one of the most common preventable causes of intellectual disability.
2. Newborn screening results in early treatment and diagnosis, potentially reducing the risk of irreversible intellectual disability and other comorbidities.
3. Clinicians should have a high clinical suspicion for congenital hypothyroidism, even with a normal result on newborn screening, because certain forms of central hypothyroidism or milder forms of primary congenital hypothyroidism may be missed.

Abstract

Congenital hypothyroidism (CH) is one of the most common preventable causes of intellectual disability. Thyroid hormone is required for normal brain development, but neonates with CH typically appear healthy at birth, which leads to delays in diagnosis and treatment. In developed countries, newborn screening programs have led to earlier diagnosis and treatment of CH, resulting in improved neurodevelopmental outcomes. Neonates with an abnormal newborn screen require prompt confirmatory serum thyroid function tests and treatment with thyroid hormone. Further evaluation for the etiology of CH should not delay treatment decisions.

Objectives After completing this article, readers should be able to:

1. Interpret newborn screening results, recognize the importance of early screening, and describe the treatment of congenital hypothyroidism.

AUTHOR DISCLOSURE Drs Weiner, Oberfield, and Vuguin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CH	congenital hypothyroidism
FT_4	free T_4
HPT	hypothalamic-pituitary-thyroid
LT_4	levothyroxine
MRI	magnetic resonance imaging
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroxine-binding globulin
TRAbs	thyrotropin receptor antibodies
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone (thyrotropin)

INTRODUCTION

Congenital hypothyroidism (CH) refers to a group of disorders that result in decreased circulating biologically active thyroid hormone. The incidence of CH in iodine-sufficient areas is approximately 1 in 3,000 to 1 in 4,000 live births, with variation worldwide. (1) Evidence from newborn screening programs in the

United States reports an incidence of 1 in 2,372 live births in 2002, increased from 1 in 4,097 in 1987. These programs have found that the incidence is higher in Hispanic and Asian neonates and lower in black neonates. (2)(3) The incidence is nearly 1.5–2:1 in female versus male neonates, and is also higher in twin births, older mothers, and preterm infants. (2)(3)(4)(5)(6) The reasons for this rise in overall incidence of CH is thought to be multifactorial and related to changes in the screening cutoffs resulting in increased detection of milder cases, increased screening of preterm infants, and increased birth of Hispanic and low-birth-weight infants. (1)(3)

The initial symptoms of CH are nonspecific because of the subtle features and protective effects of maternal hormone on the fetal brain. As the affected neonate ages, the degree of hypothyroidism worsens, increasing the risk of significant irreversible brain damage. Newborn screening, initially piloted in 1974, has resulted in earlier diagnosis and treatment of CH. Neonates with an abnormal newborn screening result should have confirmatory testing and begin levothyroxine (LT_4) treatment promptly to improve growth and neurodevelopmental outcomes. (7)

THYROID PHYSIOLOGY

Thyroid hormone plays an important role in energy metabolism, control of body temperature, growth, bone formation, and the development of the central nervous system. Specifically, thyroid hormone acts on neuronal differentiation, synapsis development, and myelination in the prenatal and newborn periods, regulating neurodevelopment. (8) There are 2 active thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). Both T_4 and T_3 are secreted by the thyroid gland, though the majority of circulating T_3 is derived from peripheral tissue deiodination of T_4. Deiodination of T_4 to T_3 is catalyzed by a group of enzymes known as iodothyronine deiodinases. Active thyroid hormone T_3 binds to the thyroid hormone receptors (TRα or TRβ) and affects the expression of thyroid hormone–dependent genes.

The hypothalamic-pituitary-thyroid (HPT) axis works to maintain a stable concentration of thyroid hormone. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the thyrotropic cells of the pituitary to produce thyroid-stimulating hormone (TSH), also referred to as *thyrotropin.* TSH then stimulates the thyroid follicular cells to produce T_4 and T_3. Hypofunctioning of the thyroid gland typically results in increases in TRH and TSH production, except in cases of pituitary or hypothalamic dysfunction (central hypothyroidism) and pituitary resistance to thyroid hormone feedback.

The fetal thyroid gland becomes visible at the fourth week of gestation and begins trapping iodine at 10 weeks' gestation. (9) In the first trimester, most of the active fetal thyroid hormone results from maternal thyroid hormone crossing the placenta. Maternal hypothyroidism alone during early gestation is a significant risk factor for impaired psychomotor development. (10) The fetal HPT axis becomes active at about 18 weeks' gestation and then functions independent of the pregnant woman, with negligible TSH placental transfer. (11) T_4 levels steadily rise after 18 weeks of gestation and T_3 levels rise after 30 weeks of gestation. In healthy term infants, there is a surge in TRH and TSH production shortly after birth, which has been attributed to cold exposure, leading to a rise in both T_4 and T_3 levels in the first 24 to 36 hours after birth. (12)(13) Figure 1 summarizes the changes in serum TSH and T_4 concentrations during the first 5 days of age.

ETIOLOGY OF CH

Most infants with CH are healthy at birth because of a small amount of placental transfer of maternal T_4. In addition, intracerebral T_4 to T_3 conversion is increased, leading to availability of brain T_3, despite low serum concentrations of T_4. (11) T_4 has a half-life of 7 to 10 days, so the signs and symptoms of CH become more apparent as maternal T_4 is metabolized. However, when both maternal and fetal hypothyroidism are present, there are significant neurointellectual delays despite adequate diagnosis and treatment. This may occur in the setting of severe iodine deficiency or potent blocking TSH receptor antibodies (TRAbs). (10)

The American Academy of Pediatrics (AAP) guidelines from 2006 dictate that "infants with low T_4 and elevated TSH concentrations have CH until proven otherwise. All

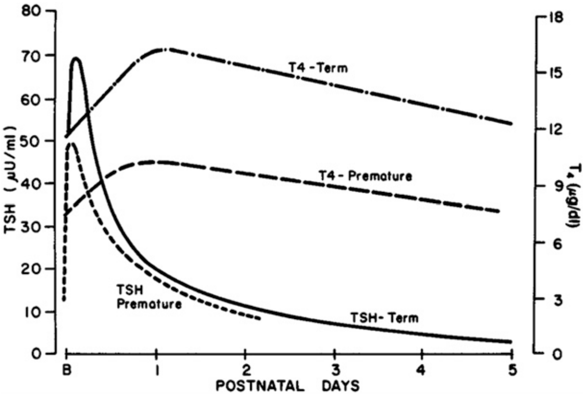

Figure 1. Changes in serum thyroid-stimulating hormone (TSH) and thyroxine (T_4) concentrations in full-term and premature infants during the first 5 days of age.

infants with hypothyroidism, with or without goiter, should be rendered euthyroid as promptly as possible by replacement therapy with TH (thyroid hormone)." (14)

Neonates with primary CH have an elevated TSH, with low T_4, T_3, and free T_4 (FT_4) values. In iodine-sufficient areas, 95% of cases of CH are primary, meaning they result from abnormalities of the thyroid gland. Although some cases are transient, such as with the presence of TRAbs, treatment should be started until the underlying etiology disappears and should not be delayed for diagnosis. Thyroid dysgenesis, failure of the thyroid gland to appropriately develop, accounts for 85% of primary CH. (15) Thyroid ectopy is usually sporadic and accounts for two-thirds of the cases of thyroid dysgenesis. It is more common in females, with a lingual thyroid representing 90% of cases. Thyroid agenesis and thyroid hypoplasia cause the other one-third of cases of thyroid dysgenesis. (15)(16) Mutations have been reported in some transcription factor genes that regulate thyroid gland development, but a genetic mutation is only found in 2% to 5% of cases of thyroid dysgenesis. (17) Thyroid dyshormonogenesis, because of a defect in the enzymes or transporters involved in thyroid hormone production, accounts for up to 10% to 15% of cases and is typically inherited in an autosomal recessive pattern. (18) Mutations in the thyroid peroxidase gene are the most prevalent form of inherited CH. Other causes include defects in peripheral thyroid hormone transport, metabolism, or action. (16) Neonatal hyperthyrotropinemia occurs when patients have a normal T_4 and FT_4 and mildly elevated TSH. These newborns require close follow-up until their TSH value normalizes, but may not require treatment.

Neonates with central CH have a low-normal TSH with low T_4, T_3, and FT_4 values. Central hypothyroidism is caused by deficient TSH production in the setting of a normal thyroid gland. The incidence of central hypothyroidism is 1 in 25,000 to 50,000 live births. (15) Central hypothyroidism is more challenging to diagnose, because human chorionic gonadotropin stimulates the normal fetal thyroid gland and thyrotrope function is not completely absent in most cases. It can be caused by various disorders affecting the hypothalamus or pituitary gland. Genes leading to TSH deficiency can be isolated or result in multiple pituitary hormone deficiencies (such as deficiency of adrenocorticotropin, growth hormone, and gonadotropins). (19) If there are signs of multiple pituitary deficiencies (micropenis and undescended testicles from luteinizing hormone deficiency and hypoglycemia from cortisol and/or growth hormone deficiency) or midline facial defects, brain magnetic resonance imaging (MRI) should be performed to assess for an absent or hypoplastic pituitary gland or abnormalities in the pituitary stalk. Septo-optic dysplasia can manifest with CH and should be considered in the presence of pituitary deficiencies, visual defects and/or blindness, congenital nystagmus, and midline brain defects. Multiple pituitary abnormalities may reflect a genetic defect in pituitary formation, such as *PROP1*, *LHX3*, or *Pou1F1* mutations. (16) If isolated, central hypothyroidism typically results from a mutation in the beta subunit of the *TSH* gene or *TRH* receptor gene. (15) Brain trauma, asphyxia, and excessive treatment of maternal hyperthyroidism can also lead to central hypothyroidism. Neonates with central hypothyroidism may have similar laboratory values as neonates who are premature, critically ill, or have thyroxine-binding globulin (TBG) deficiency.

Preterm and critically ill infants have a smaller rise in TSH, T_4, T_3, and FT_4 at birth compared with healthy term infants, because of immaturity of the HPT axis and nonthyroidal illness (sick euthyroid syndrome). The reference range for thyroid hormones varies by gestational and postnatal age. Preterm infants may also have lower concentrations of TBG. During the first week after birth, there is a decline in T_4 levels, which is greater in very-low-birthweight and more premature infants. Preterm or critically ill infants with low T_3 and T_4 levels and normal TSH levels on initial evaluation typically have normalization of the thyroid function by 6 to 10 weeks after birth without needing treatment. Van Wassenaer et al showed that neonates who were treated with T_4 at less than 27 weeks' gestation had improvement in mental development scores at 2 years of age and motor development outcomes at 10.5 years of age; however, when T_4 was administered to neonates at 27 weeks' gestation or later, treated infants had worse neurodevelopmental outcomes than those who received a placebo. (20)(21) Currently, there is insufficient evidence to recommend treating preterm infants with abnormal thyroid function. However, preterm and critically ill infants require close monitoring because there may be a delay in the appropriate TSH elevation in cases of transient or permanent primary hypothyroidism, thus leading to a delay in diagnosis and treatment of CH. (22)

A low total T_4 with normal TSH and FT_4 levels in a healthy infant may indicate TBG deficiency. This is an X-linked disorder with an incidence of 1 in 4,000 males. There is no true deficiency, so treatment is not needed. (15) Rarely, a neonate may have primary hypothyroidism and TBG deficiency. In these cases, the TSH will be useful in determining the accurate diagnosis.

Transient hypothyroidism can be seen with maternal blocking TRAbs, exposure to maternal antithyroid medications, iodine deficiency or excess, and large congenital hepatic hemangiomas (increased type 3 deiodinase activity). (15) TRAbs, as seen in maternal Graves' disease, cross the placenta and can block or mimic the function of TSH. Neonatal Graves' disease (also called neonatal autoimmune hyperthyroidism) occurs in about 2% of neonates born to mothers with Graves' disease and may be associated with serious neonatal adverse events, including goiter, intrauterine growth restriction, oligohydramnios, prematurity, tachycardia and heart failure, hepatomegaly, and death. (23) Alternatively, hypothyroidism from maternal Graves' disease has an incidence of 1 in 180,000. The antibodies typically disappear from the serum of the affected infant by 3 to 5 months of age. (24)

In developing countries, iodine deficiency continues to be a significant cause of preventable cognitive deficits. Selenium and iron deficiencies may have an effect on neurologic development and thyroid response to iodine. (14) Iodine exposure with surgery and procedures can increase the risk of hypothyroidism secondary to iodine overload. This is usually transient but short-term therapy may be needed. (15)

Patients with Down syndrome have a mild increase in TSH concentration, with lower mean FT_4 values than the general population. Down syndrome is associated with higher rates of thyroid dysfunction, most commonly subclinical hypothyroidism and thyroid autoimmunity. The AAP recommends routine newborn screening at birth and then serum thyroid screening at 6 months, 1 year, and then annually in children with Down syndrome. (25)

CLINICAL FINDINGS AND DIAGNOSIS OF CH

The majority of cases of CH are asymptomatic at diagnosis. Symptoms may include increased sleep, constipation, and poor/slow feeding. On examination, neonates may have macroglossia, an umbilical hernia, dry skin, a coarse puffy face, and a widened anterior fontanelle with delayed reflexes and hypotonia on neurologic examination. In some cases of thyroid dyshormonogenesis, a goiter may be palpable. Prolonged neonatal jaundice, specifically conjugated hyperbilirubinemia, should be an indication to evaluate thyroid function as well as to assess for panhypopituitarism. If performed, radiography may reveal an absent femoral epiphysis because of delayed skeletal maturation in patients with severe hypothyroidism. (16)

Screening for early detection of primary hypothyroidism results in a diagnosis in 1 in 2,000 live births. (26) The pilot hypothyroidism screening programs were developed in Quebec, Canada, and Pittsburgh, PA, in 1974. In addition to clinical benefit, the cost or screening for CH is significantly lower than the cost of diagnosing CH at an older age. (14) The ideal time for newborn screening tests is 48 to 72 hours after birth to avoid the physiologic surge in TSH that occurs in the first hours after birth. To perform the newborn screen, capillary blood from a heel stick is placed on circles of specialized filter paper, dried, and then sent to a centralized laboratory. Figure 2 summarizes the algorithm for newborn thyroid screening. Initial screening varies by state, with 3 possible options: primary T_4 screening with reflex TSH if the T_4 value is below the cutoff, primary TSH screen, or combined TSH and T_4 screen. (15) TSH assays are becoming more accurate with small volumes of blood, so this is now the standard in most screening protocols. States with primary TSH screening may miss central hypothyroidism, while states with primary T_4 screening may miss cases of mild or subclinical hypothyroidism. (15) Samples taken within 48 hours of birth may lead to false-positive results, because the TSH value is physiologically elevated. Samples in sick newborns (with a delayed rise in TSH) or following blood transfusions may lead to false-negative results. Second screening at 2 to 4 weeks of age is becoming routine in certain programs. The addition of a second screen has diagnosed 1 in 30,000 neonates. A second screen should definitively be performed in preterm and low-birthweight infants, critically ill infants, same-sex twins, and infants with a first screen within the first 24 hours after birth. (27) However, screening should be performed before hospital discharge or a transfusion, even if it occurs before 48 hours after birth. (14) Kilberg et al reviewed the TSH cutoffs for 49 of the 50 newborn screen programs that process newborn screens received beyond the first 72 hours after birth. Of these programs, 24 do not adjust the TSH concentration cutoff according to an infant's age, and therefore cases of mild persistent CH may be missed. The use of age-adjusted TSH cutoffs in all screening programs is recommended. (28)

- TSH screening: If the TSH value is elevated (typically defined as >20–40 mU/L), confirmatory serum testing is required. A TSH value <20 mIU/L in the first 72 hours after birth is considered normal.
- Primary T_4 screening: If the T_4 value is less than the 10th percentile of the cutoff for all newborn screens that are done that day, TSH is performed on the same filter paper. If the TSH is not elevated, most screening programs require no further follow-up. States that require follow-up will either request a second newborn screening test or recommend confirmatory serum testing. If the TSH is elevated, confirmatory serum testing is required.

If the newborn screen is positive, venipuncture blood is required to confirm the diagnosis of CH. Confirmatory serum tests should ideally be obtained in the first 2 weeks of age. Serum samples should be sent to measure the TSH level and either a total T_4 or FT_4 level. The total T_4 test is less expensive and can be reported within hours; however, FT_4 values are not affected by changes in TBG and represent the biologically relevant T_4. The results should be compared with age-normalized values for full-term and preterm infants. Prompt consultation with a pediatric endocrinologist is recommended if the results are abnormal for age. The TSH concentration is the most sensitive indicator of the HPT axis. Before age 2 weeks, venous TSH values greater than 20 mIU/L, and after 2 weeks, TSH values greater than 10 mIU/L suggest primary CH. Low serum T_4 or FT_4 with an elevated TSH confirms the diagnosis of primary hypothyroidism and treatment should be started immediately.

For subclinical hypothyroidism (also referred to as *hyperthyrotropinemia*) with a TSH value between 6 and 20 mIU/L with normal FT_4, it is reasonable to proactively monitor serum thyroid tests closely and defer starting LT_4 unless the TSH level continues to rise or the FT_4 level decreases to below normal.

As discussed earlier, there is no clinical evidence that thyroid hormone treatment is beneficial for preterm infants with physiologic hypothyroxinemia or hyperthyrotropinemia. Although some of these infants have a low T_4 level and a low or normal TSH level on the initial newborn screen, most will have normal results on the second or third newborn screen.

Additional investigations to identify the cause of the CH should not delay treatment decisions, though it may be useful for future decision making. Thyroid ultrasonography is usually the first test performed to determine the etiology of primary hypothyroidism. Color Doppler may be useful to identify an ectopic thyroid gland. An iodine uptake scan, with iodine 123 or sodium pertechnetate 99m, is the most accurate imaging tool to determine the size and location of

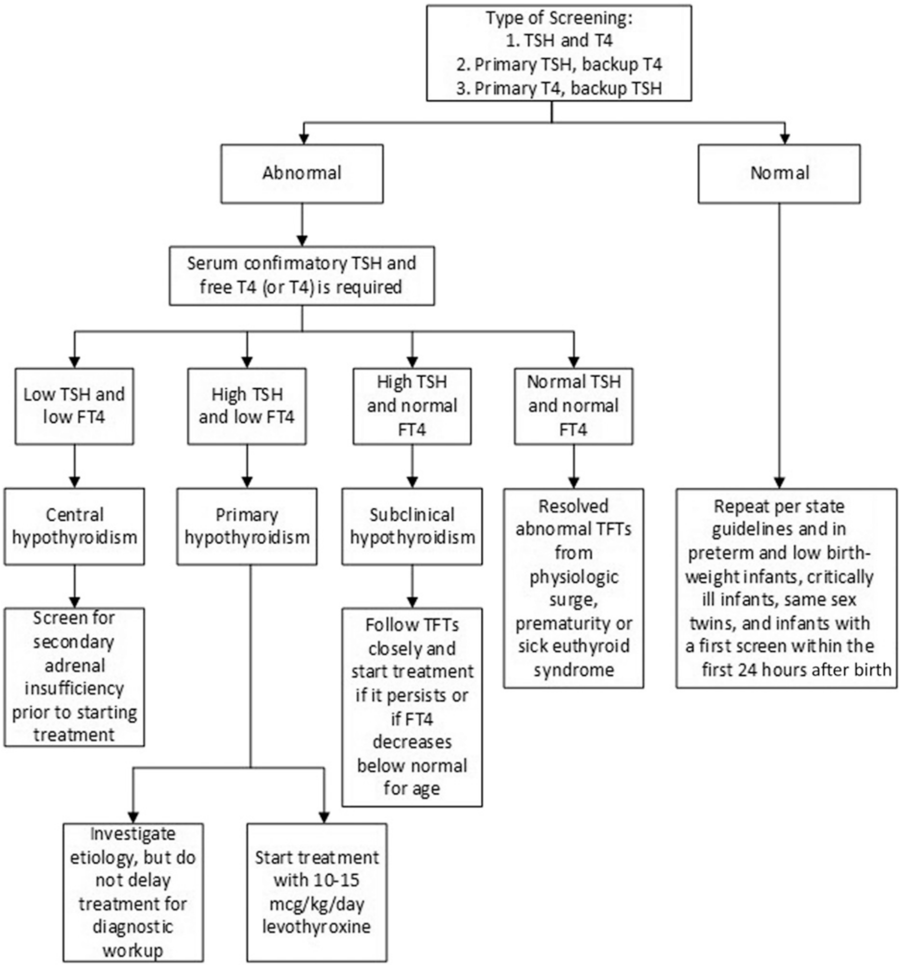
Type of Screening:
1. TSH and T4
2. Primary TSH, backup T4
3. Primary T4, backup TSH
Abnormal
Normal
Serum confirmatory TSH and free T4 (or T4) is required
Low TSH and low FT4
High TSH and low FT4
High TSH and normal FT4
Normal TSH and normal FT4
Central hypothyroidism
Primary hypothyroidism
Subclinical hypothyroidism
Resolved abnormal TFTs from physiologic surge, prematurity or sick euthyroid syndrome
Repeat per state guidelines and in preterm and low birth-weight infants, critically ill infants, same sex twins, and infants with a first screen within the first 24 hours after birth
Screen for secondary adrenal insufficiency prior to starting treatment
Follow TFTs closely and start treatment if it persists or if FT4 decreases below normal for age
Investigate etiology, but do not delay treatment for diagnostic workup
Start treatment with 10-15 mcg/kg/day levothyroxine

Figure 2. Newborn screening algorithm for congenital hypothyroidism. FT_4=free thyroxine; TSH=thyroid-stimulating hormone; T_4=thyroxine.

the thyroid tissue. (29) It can be used to diagnose thyroid aplasia, hypoplasia, or an ectopic gland. Patients with blocking TRAbs, TSH receptor inactivating mutations, and iodine trapping defects will also not show any uptake but will have a normal or enlarged thyroid on ultrasonography. Alternatively, thyroglobulin levels may also be used to assess for the presence of a thyroid gland.

If the diagnosis of central hypothyroidism versus sick euthyroid is in question, testing for reverse T_3 or FT_4 levels with equilibrium dialysis measurements may be useful. (19) Patients with sick euthyroid syndrome typically have an elevated reverse T_3 level because of decreased metabolism of T_3. For patients found to have central hypothyroidism, it is crucial to screen for other pituitary deficiencies and to perform brain MRI.

If iodine excess or deficiency is a concern, a test of the infant's 24-hour urine iodine excretion may be useful, though challenging to obtain in neonates. The normal range is 50 to 100 mg/24 hours. (15)

In the setting of maternal Graves' disease, van der Kaay et al recommended using a neonatal Graves' risk assessment algorithm for neonates, based on the presence of maternal TRAbs. (23) If maternal serum TRAbs are positive or unknown, the TRAb level should be obtained from the cord blood or the neonate. Neonates with unknown or positive TRAb levels should be examined on the first day after birth, with follow-up examination and laboratory testing for TSH and FT_4 at 3 to 5 and 10 to 14 days of age. At that point, asymptomatic neonates with normal thyroid function can have routine follow-up at 1 month and 2 to 3 months of age. If the TRAb level is negative in the pregnant woman in the second or third trimester or from the cord/infant blood, the neonate is considered at low risk with no specific follow-up needed. If the thyroid function is abnormal or the newborn has clinical signs of hypo- or hyperthyroidism, prompt consultation with pediatric endocrinology is required for further management. (30)

MANAGEMENT OF CH

The timing and dosing of thyroid hormone replacement is crucial for neurodevelopment. LT_4 at 10 to 15 μg/kg per day is recommended and should be administered 30 minutes before feeding. The absorption is hindered by food and products with soy, iron, calcium, and aluminum. A crushed LT_4 tablet is typically mixed with 1 to 2 mL of breast milk, formula, or water and the suspension is placed in the cheek pad. Recently, a commercial levothyroxine sodium oral solution has been made available for the treatment of hypothyroidism and pituitary TSH suppression. It is the first liquid formulation of LT_4 approved by the Food and Drug Administration. However, the treatment of choice continues to be the tablet form of LT_4. If intravenous therapy is needed, the dose should be 50% to 80% of the oral dose. (31)

Treatment should be initiated within 2 weeks from birth. However, in patients with adrenal insufficiency in addition to central hypothyroidism or in those in whom adrenal insufficiency cannot be excluded, assessment of adrenal function, followed by adequate glucocorticoid therapy is needed for 48 to 72 hours before supplementing with LT_4, to prevent inducing an adrenal crisis.

The AAP recommends monitoring thyroid function 2 and 4 weeks after initiation of LT_4 treatment and every 1 to 2 months during the first 6 months of age. The goal is to normalize T_4 and TSH within 2 and 4 weeks, respectively. (14)(32) The target is T_4 and FT_4 concentrations in the upper half of the reference range for age, with normalization of TSH. (14)

Infants should be examined carefully for dysmorphic features, because congenital abnormalities are more common in patients with CH than in the general population. These abnormalities most commonly include heart defects, sensorineural hearing loss, or dysmorphic features. (15) Patients with syndromic features or a family history of hypothyroidism should be referred to genetics for further evaluation. For example, Pendred syndrome, from a defect in pendrin, which is a transmembrane chloride-iodide transporter, results in sensorineural deafness, hypothyroidism, and goiter. Bamforth-Lazarus syndrome is caused by a mutation in thyroid transcription factor 2 and results in thyroid dysgenesis, choanal atresia, cleft palate, and spiked hair. (16)

Early detection and treatment of CH results in a near normal IQ, though mild brain impairment and discordance with family mental functioning may exist. The average IQ is approximately 6 points below expected, and there may be deficits in visuospatial, motor, language, memory, and attention tests. Mild sensorineural hearing loss also may be seen in up to 20% of cases. (33) Discontinuation of thyroid treatment before 3 years of age is not recommended. (26) For central hypothyroidism, cognitive deficits can be particularly severe if there is a delay in diagnosis. (19) Patients should be screened for problems with hearing and visual processing as well as for speech delay and referred to therapy if there are any concerns before 3 years of age. (31)

If there is no identified permanent cause of CH and no TSH increase after the newborn period with LT_4 treatment, the treatment should be discontinued after the child is 3 years old. The FT_4 and TSH should be measured 30 days later to determine if the child is euthyroid without the medication. If the TSH is elevated at 30 days, permanent hypothyroidism is diagnosed and LT_4 treatment should be resumed. If the results are inconclusive, repeat testing is needed. (14) Patients successfully weaned off LT_4 continue to require follow-up, while patients with permanent CH require LT_4 treatment for life.

SUMMARY

- Nationwide screening programs are the best method to diagnose CH (evidence level A). (14)(31)
- Diagnosis and treatment should be made in the first few weeks of age for optimal neurodevelopmental outcomes (evidence level A). (7)
- Imaging and further diagnostic evaluation should never delay treatment decisions (evidence level A). (14)(15)
- A clinical suspicion for hypothyroidism should be maintained in the right clinical setting, regardless of newborn screening results (evidence level A). (14)
- Repeat newborn screening should be performed in sick or premature infants at 3 to 4 weeks of age or before hospital discharge (evidence level A). (27)

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function.
- Know the relationship between fetal and maternal thyroid physiology.
- Know the embryology and normal physiological function of the thyroid gland.
- Know the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction.
- Know the etiology and clinical manifestations of congenital hypothyroidism.
- Know the laboratory features and approach to therapy of congenital hypothyroidism.
- Know how to evaluate and manage the causes of transient hypothyroidism in newborn infants.
- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis.

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1 Persistent Hypoglycemia in a 46,XX Newborn with Ovarian Dysgenesis

Sarah Yavelberg, MD,* Omer Choudry, MD,* Arun K. Kashyap, MD,*
Danitza M. Velazquez, MD*

*Department of Pediatrics, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ

PRESENTATION

A 4-day-old female newborn is transferred from an outside hospital for further evaluation and management of hypoglycemia. She had been born at 37 weeks' gestation to a 23-year-old gravida 2, para 1 woman via spontaneous vaginal delivery. The prenatal history was unremarkable. She had a birthweight of 2,815 g (50th percentile) and length of 47 cm (40th percentile). She was initially discharged from the hospital on day 2 after birth. On day 4, she is brought back to the emergency department after 5 episodes of watery, nonbloody diarrhea and nonbloody, nonbilious emesis at home. In the emergency department, her vital signs are within the normal range for age. She is found to be hypoglycemic, with a blood glucose level of 31 mg/dL (1.7 mmol/L) for which she received a bolus of 10% dextrose in water. The repeat glucose level after the bolus is 84 mg/dL (4.6 mmol/L) and she is subsequently transferred to the NICU.

On arrival at the NICU, her admission vital signs are within the normal range for age, and physical examination reveals a moderately dehydrated, nondysmorphic infant who is alert and fussy. She has jaundice to the umbilicus and a mongolian spot near her sacrum. The remainder of her physical examination findings are within the range for age. Her blood glucose concentration is 53 mg/dL (2.9 mmol/L). Her admission blood gas measurements and complete blood cell counts are unremarkable. She is started on 10% dextrose water in addition to feedings of expressed breastmilk and supplemental infant formula as needed, at least every 3 hours. Blood and stool cultures are sent and prophylactic antibiotics initiated. Total and direct bilirubin concentrations are normal—9.6 mg/dL (164.2 μmol/L) and 0.3 mg/dL (5.1 μmol/L), respectively. Antibiotics are discontinued after the blood culture is found to be negative for 48 hours. Stool viral culture is also negative. She is weaned off intravenous dextrose support by hospital day 2 but the preprandial blood glucose again drops as low as 48 mg/dL (2.6 mmol/L), which improved with feeding. Endocrinology and genetics services are consulted. Endocrinology recommends drawing critical laboratory samples, which are drawn with a subsequent hypoglycemic episode. Results of the evaluation for hypoglycemia as requested by endocrinology and genetics are shown in the Table.

Magnetic resonance imaging (MRI) of the brain is performed to evaluate the pituitary gland, and findings appear to be within normal limits. Pelvic ultrasonography is performed, given the elevated follicle-stimulating hormone level and concern for Turner syndrome; the uterus is seen to be normal for age but the ovaries could not be visualized. Because of the failure to identify the ovaries, Turner syndrome is a concern. Echocardiography reveals a trivial midmuscular

AUTHOR DISCLOSURE Drs Yavelberg, Choudry, Kashyap, and Velazquez have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Choudry's current affilation is Department of Pediatrics, Lehigh Valley Hospital, Allentown, PA.

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TABLE. **Results of Evaluation for Hypoglycemia**

LABORATORY TEST	PATIENT RESULT (SI UNITS)	COMPARED WITH NORMAL VALUES
Ammonia	123 μg/dL (87.8 μmol/L)	slightly elevated
β-hydroxybutyrate	5.4 mg/dL (520 μmol/L)	high
Insulinlike growth factor–binding protein 3	0.8 μg/mL	high
C-peptide	0.4 ng/mL (0.13 nmol/L)	low
Growth hormone	4.98 ng/mL (4.98 μg/L)	normal
PM cortisol	17 μg/dL (469 nmol/L)	high
Thyroid-stimulating hormone	3.32 mIU/L	normal
Free thyroxine	2.34 ng/dL (30 pmol/L)	slightly elevated
Follicle-stimulating hormone	30.0 mIU/mL	high
Prolactin	253 μg/L (11,000 pmol/L)	high
Lactate dehydrogenase	4.9 IU/L (0.08 μkat/L)	normal
Estradiol	<10 pg/mL (<36.7 pmol/L)	normal

ventricular septal defect with restrictive left-to-right shunt but was otherwise normal. Karyotyping reveals a 46,XX normal female karyotype. Pelvic MRI to follow up the ultrasound results confirms a normal neonatal uterus but also fails to visualize ovaries.

The patient continues to feed a combination of expressed breast milk and infant formula. Preprandial blood glucose levels remain above 58 mg/dL (3.2 mmol/L) over the remaining course of her hospital stay and normalize to levels greater than 60 to 70 mg/dL (3.3–3.9 mmol/L) in the days leading up to her discharge. She does not receive correction for her low blood glucose other than her normal feeds. She is discharged on day 18 after birth with a glucometer and the parents are instructed on using glucagon for severe hypoglycemia.

On outpatient follow-up with endocrinology, the infant is scheduled to have a repeat pelvic ultrasonography around 4 to 6 months of age to reevaluate for the presence of ovaries. No further episodes of hypoglycemia have been reported and the family has not needed to administer glucagon. Outpatient genetics follow-up has not been arranged and no further genetic testing has been ordered until after outpatient endocrinology follow-up.

DISCUSSION

Gonadal dysgenesis may occur in a female infant with a normal (46,XX) karyotype because of a genetic defect, fetal exposure to endocrine disruptors, or gonadal regression. Normal sex development begins similarly in male and female embryos before 6 weeks of gestation. The genital ridge becomes either ovaries or testes based on the sex chromosomes (46,XX or 46,XY). (1) If the Y chromosome is absent, ovaries normally develop at 11 to 13 weeks' gestation. If the Y chromosome is present, the sex-determining region on Y (*SRY*) gene located on the short arm of the Y chromosome directs the testes to develop at 6 weeks' gestation. The *SRY* gene codes for the production of sex-determining factor, which leads the genital ridge to develop into Sertoli or Leydig cells. Sertoli cells secrete müllerian inhibiting substance (MIS), which causes the regression of the müllerian ducts, while Leydig cells secrete testosterone, which directs the maturation of spermatogonia and male external genitalia. Sex ducts become müllerian ducts, which in the absence of MIS become the uterus, fallopian tubes, and upper vagina, and wollfian ducts, which in the presence of MIS become the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts. The germ cells become ova or spermatogonia.

Hypoglycemia has been reported in the setting of gonadal dysgenesis in a few case reports, most of which present in infant girls with XO karyotype. Glassman et al described 2 female infants with hypoglycemia that was aggravated by the administration of leucine. (2) The authors concluded that the occurrence of leucine-sensitive hypoglycemia in patients with Turner syndrome provides evidence of pancreatic dysfunction in patients with X chromosomal abnormalities.

Genetic defects responsible for gonadal dysgenesis and disorders of sex development (DSD) include defects in the

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SRY gene as well as Turner syndrome (45,XO) and ovotesticular disorders of sex development. In 80% of testicular DSD, the *SRY* gene is translocated from the Y chromosome onto the X chromosome and is therefore present in a 46,XX fetus. In 46,XX testicular DSD without the presence of the *SRY* gene, a gene mutation may be seen in the testis-differentiating pathway or a hidden Y mosaicism. In ovotesticular DSD, ovarian and testicular tissue are both present in the gonads. These individuals typically have a 46,XX genotype, but may rarely have a 46,XY, 46,XX/46,XY, or 45,XO/46,XY mosaicism. This diagnosis is confirmed with gonadal biopsy showing both ovarian and testicular tissue. Although Turner syndrome is most commonly diagnosed with 45,XO karyotype, some individuals may have a 45,XO/46,XX mosaicism not represented in the sample tested. Röpke et al studied patients with sex-chromosomal mosaicism in gonads but normal karyotypes in lymphocytes. (3) They recommend cytogenetic and fluorescence in situ hybridization analyses of gonadal tissue to confirm the diagnosis.

Gonadal dysgenesis with normal female karyotype (46,XX) has been described in few studies. In 1994, Aittomäki described a nationwide population-based study in Finland of women born between 1950 and 1976, of whom 75 were found to have XX gonadal dysgenesis. (4) In 1 family, 4 daughters were affected; in 6 families, 2 daughters were affected; and 57 cases were isolated. Consanguinity was detected in 12% of families (8 of 66). These findings led the authors to conclude that an autosomal recessive XX gonadal dysgenesis exists. In 1996, Meyers et al analyzed families having at least 2 female offspring. (5) In these patients, ovarian failure was documented by the presence of streak ovaries or elevated gonadotropins. They determined that given the distribution of patients in these families, many 46,XX females with ovarian dysgenesis likely represent an autosomal recessive trait. They noted that some of these females had only gonadal signs, while others also had neurosensory hearing loss, representing Perrault syndrome.

Females with Perrault syndrome often have abnormal or absent ovaries, though external genitalia are normal. (6) Most affected females do not menstruate, though women with a milder form can have early loss of ovarian function with normal menstrual periods beginning in adolescence and becoming less frequent in the subsequent decades. Sensorineural hearing loss is bilateral and ranges from profound congenital hearing loss to moderate early-childhood onset hearing loss that can be progressive. Neurologic features described in some individuals with Perrault syndrome include learning difficulties and developmental delay, cerebellar ataxia, and motor and sensory peripheral neuropathy. The diagnosis of Perrault syndrome is based on the clinical findings of sensorineural hearing loss in men and sensorineural hearing loss with concomitant ovarian dysfunction in women with a 46,XX karyotype. The diagnosis is confirmed by the presence of biallelic mutations in 1 of 6 genes (*CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS1*, or *TWNK*), though in approximately 60% of patients with Perrault syndrome identified to date, results of genetic testing are negative.

Fetal exposure to environmental and other endocrine disrupting chemicals should be considered if no genetic mutation is found. These agents include antiandrogens such as flutamide, vinclozolin, 1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene (DDE), and 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane (DDT); exogenous estrogen from diethylstilbestrol, ethinyl estradiol, and bisphenol A; and phthalates. In 1985, Yasuda et al demonstrated that mice exposed to ethinyl estradiol between days 11 and 17 of gestation were born with ovotestis consisting of testicular and ovarian portions. (7) A 2014 review by Costa et al notes that bisphenol A (BPA) has the strongest effects on thyroid hormones as well as estrogenic and adipogenic activity. (8) Pesticides also have effects on estrogen signaling, and can promote changes in the reproductive system, sexual differentiation, and pubertal changes.

Gonadal regression in neonates is rare but is most often caused by gonadal torsion. In 2013, Mneimneh et al noted that total gonad regression occurred only in cases of neonatal testicular torsion, while necrotizing palisaded granulomatas are uniquely encountered in ovarian torsion and regression. (9) They noted patients of both sexes had findings of calcifications, siderophages, and fibrosis, in addition to tissue necrosis.

Lessons for the Clinician

- Hypoglycemia has been reported in the setting of gonadal dysgenesis in a number of case reports, but mostly with an XO genotype.
- Gonadal dysgenesis with normal female karyotype (46,XX) has been described in a few studies and likely represents an autosomal recessive trait.
- Perrault syndrome is a condition with an XX genotype in which females may present with absent or abnormal ovaries along with sensorineural hearing loss and can have long-term neurological problems and developmental delays.
- Clinicians should be aware of the differential diagnosis for ovarian dysgenesis so that it can guide a proper diagnostic evaluation.

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- Know the etiology of abnormal sexual differentiation.
- Know the diagnostic approaches to and management of abnormal sexual differentiation.

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Case 1: Persistent Hypoglycemia in a 46,XX Newborn with Ovarian Dysgenesis

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2 Newborn with Hemorrhagic Skin Reaction

Katherine Redford, DO,* Gina M. Trachimowicz, MD*

*Barbara Bush Children's Hospital, Portland, ME

PRESENTATION

A female infant is born via emergent repeat cesarean section because of a maternal abruption. The mother is a 34-year-old woman whose history includes 3 prior preterm cesarean deliveries and polysubstance abuse with recent use of crack cocaine a few hours before delivery. The infant was born at 27 2/7 weeks weighing 920 g.

After delivery, the infant had a spontaneous cry with poor tone, color, and respiratory effort. She was briefly given positive pressure ventilation and supported on continuous positive pressure ventilation. Apgar scores are 3 and 7 at 1 and 5 minutes, respectively. Physical examination findings were unremarkable. She was placed in a plastic bag for thermoregulation and reduction of insensible water losses.

As per routine procedure, she received erythromycin eye ointment and prophylaxis against hemorrhagic disease of the newborn with an intramuscular injection of 0.5 mg vitamin K in her upper left thigh (vastus lateralis muscle) using a 26-gauge, 5/8" needle approximately 90 minutes after birth. Intravenous access was established, and she was started on treatment with ampicillin and gentamicin for presumed early-onset sepsis. Her respiratory distress worsened, and she underwent endotracheal intubation with a 2.5-mm tube and was given 1 endotracheal dose of surfactant for the treatment of respiratory distress syndrome. Because of hypotension, she received a normal saline bolus (10 mL/kg) with improvement in her blood pressure.

Approximately 45 minutes after the vitamin K injection, she developed a well-defined ecchymotic area measuring 4×2.5 cm (Fig 1 and Fig 2). Within a few hours, edema, skin splitting, and serosanguinous drainage developed, mostly on the proximal edge.

DISCUSSION

Differential Diagnosis

Differential diagnosis for an evolving ecchymotic skin lesion includes infiltrate of intravenous medication, cutaneous reaction to injection (Nicolau syndrome), birth or intrauterine trauma, subcutaneous opportunistic fungal infection, and compartment syndrome.

Actual Diagnosis

Given the close temporal relationship to the vitamin K injection, Nicolau syndrome was thought to be the most likely diagnosis. Examination demonstrated adequate peripheral perfusion, reassuring against compartment syndrome, a rare complication of Nicolau syndrome. Given that it evolved further after birth,

AUTHOR DISCLOSURE Drs Redford and Trachimowicz have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

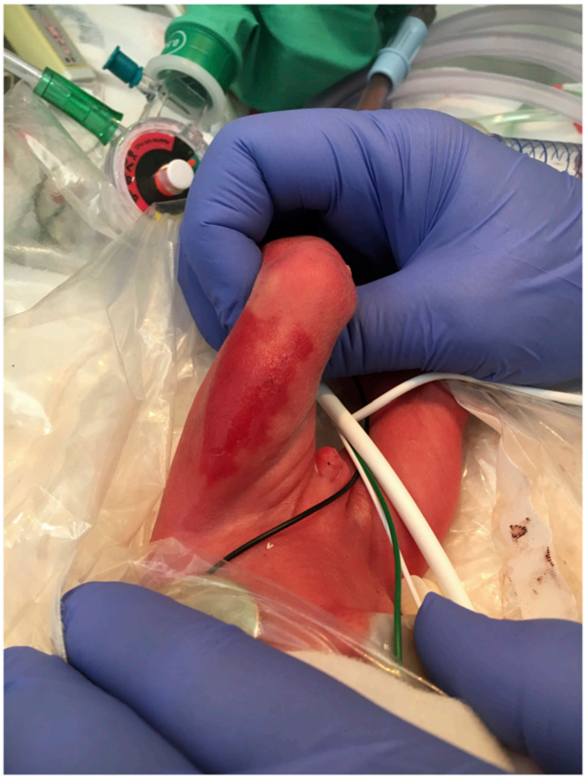

Figure 1. Initial skin changes seen at about 1 hour after vitamin K injection.

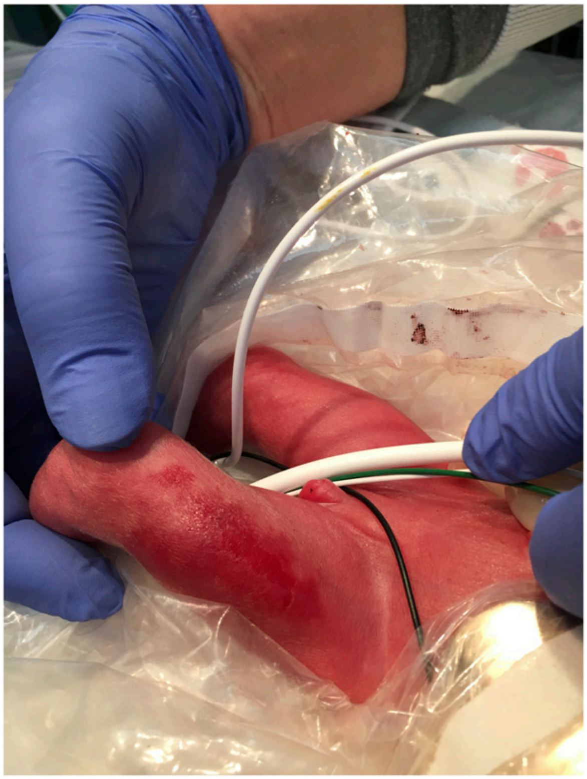

Figure 2. Initial skin changes seen at about 1 hour after vitamin K injection.

intrauterine and delivery trauma seemed less likely. Development on the first day after birth made opportunistic fungal infection less likely, even in a premature neonate.

The Condition

Nicolau syndrome (also called "embolia cutis medicamentosa" or "livedoid dermatitis") is a cutaneous reaction to an injection that is given in an intravascular or perivascular route rather than intramuscular, as intended. Many agents have been implicated in Nicolau syndrome. Some examples include immunotherapy (allergy injections), (1) benzathine penicillin, and (2) triple diphtheria-tetanus-pertussis vaccine, (3) among others. Pathophysiology is not definitively known but likely involves occlusion or damage to arterioles causing necrosis of the surrounding tissue. (4) Immunologic response is not thought to be a contributing factor because of its occurrence in the premature infant with an immature immune system. (5)

When the patient is old enough to verbalize symptoms, Nicolau syndrome is associated with immediate and severe pain at the time of injection and subsequent exquisite tenderness at the injection site. (1) The initial skin changes of pallor and edema are almost immediate and are followed by a red-violet hemorrhagic plaque and eventual varying degrees of necrosis, ulcers, erosions, crusts, and bullae. (3) Skin biopsies demonstrate necrosis of the epidermis and thrombosis of small and medium blood vessels. (3) Magnetic resonance imaging demonstrates a small stellate region of signal change consistent with fibrotic granulation tissue. (1)

Treatment/Management

Conservative management is first-line option for this diagnosis. Antibiotics should only be used in the setting of secondary infection. (6) Topical anesthetic and steroid creams have been described to help with discomfort in older children. (3) Surgical intervention, particularly debridement and skin grafting, are rarely required.

These skin lesions heal in weeks to months and have an atrophic scar. (3) Case reports have described the use of hyperbaric oxygen to avoid scarring. (4) In 1 case report, a pediatric patient developed subsequent compartment syndrome, kidney dysfunction, seizure, and cardiorespiratory failure leading to death. (2)

Methods of prevention include aspiration before injection to decrease likelihood of perivascular or intravascular injection, sufficient depth to reach intramuscular space, and the Z-track method to decrease subcutaneous irritation. (6)

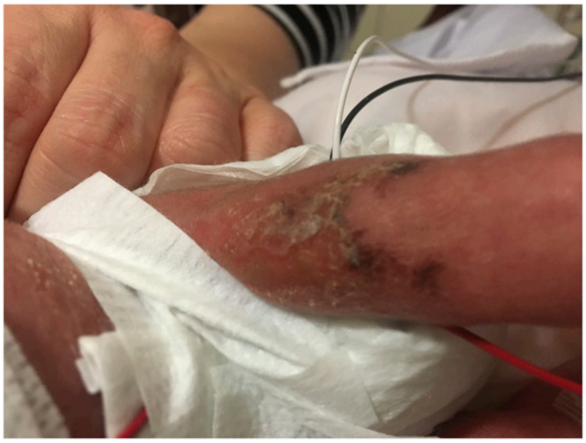

Figure 3. Skin changes a few days after birth.

Patient Course

Because of the evolving nature of the lesion and a high suspicion for an infiltrate of inadvertent medication, in the current case, hyaluronidase was given to aid in the dispersion of the unknown medication and to reduce the local concentration.

Pediatric surgery was consulted, and an additional literature search revealed the clinical diagnosis. Erythema decreased, and the skin began to slough off in the days after birth (Fig 3). The lesion slowly decreased in size and within 3 weeks, a scar remained at the site of injection.

Lessons for the Clinician

- The very sudden onset of skin changes and evolution consistent with necrosis are suggestive of the diagnosis of Nicolau syndrome. Imaging and skin biopsy are not required to make the diagnosis with the appropriate exposure history and evolution of symptoms.
- Supportive care is indicated and aside from scarring, long-term complications and escalation of interventions are rare. This should reassure clinicians that the benefit of adequate vitamin K far outweighs the risk of this potential complication of injection.
- We hope to raise awareness of this potential complication among clinicians caring for newborns and preterm newborns to avoid unneeded diagnostic tests or therapeutic interventions.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- For therapeutic drugs commonly used in the neonate (eg, opiates, methylxanthines, barbiturates, etc), know indications for their use, clinical effects, side effects, and toxicity.
- Know the complications and management of various neonatal skin injuries including IV infiltrates and chemical and thermal burns.
- Know the potential toxicity of various drugs applied topically to newborn skin, including antiseptics, lidocaine, and mydriatic agents.

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Case 2: Newborn with Hemorrhagic Skin Reaction

Katherine Redford and Gina M. Trachimowicz

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Index of Suspicion in the Nursery

3

Poor Weight Gain and Severe Dehydration in a 3-month-old Infant

Archana S. Kota, MD,* Krishan Kumar, MD,* Sehar Ejaz, MD*

*Department of Pediatrics, Nassau University Medical Center, East Meadow, NY

PRESENTATION

A 3-month-old boy presents with poor feeding and difficulty breathing for 2 days. He was born at term with a birthweight of 2.579 kg. His weight gain continues to be poor since birth. Parents noticed some weight loss 1 week before presentation. Despite significant reduction in oral intake, he continues to maintain good urine output.

On physical examination, he is ill appearing and severely dehydrated. Both length and weight are less than the third percentile. His respiratory rate is 45 breaths/min. Initial laboratory evaluation shows a blood glucose level of 810 mg/dL (44.96 mmol/L) with large serum ketones. Venous blood gas reveals metabolic acidosis, with a pH of 7.068 and bicarbonate level of 2.1 mEq/L (2.1 mmol/L). A diagnosis of diabetic ketoacidosis is made, and the patient is started on an intravenous infusion of insulin after initial fluid boluses. His glucose levels are monitored, and become stable over the next few days when he is switched to subcutaneous insulin. Autoimmune markers for diabetes are negative. Serum C-peptide level is undetectable. Fructosamine level is elevated, 159 mg/dL (888 μmol/L). Abdominal ultrasonography shows normal pancreas. Genetic testing confirms the diagnosis.

DIAGNOSIS

Based on the history and laboratory results, a diagnosis of neonatal diabetes is established.

Sequence analysis of *KCNJ11* confirms a heterozygous missense variant on Exon 1, p. (Arg201Cys) confirming a diagnosis of neonatal diabetes caused by a pathogenic variant of *KCNJ11* (Online Phenotype Mendelian Inheritance in Man [OMIM] # 606176). Sequence analysis for both parents is normal.

DISCUSSION

Neonatal diabetes is a rare form of monogenic diabetes that usually presents with hyperglycemia in the first 6 months of age. It accounts for up to 1 in 300,000 live births in the United States. It usually presents with dehydration and failure to thrive with or without ketoacidosis. It is classified into permanent and transient types. In transient neonatal diabetes, hyperglycemia usually resolves by 3 months of age. However, there is a 50% chance of reoccurrence of diabetes later in life in transient neonatal diabetes. If the diabetes fails to go into remission after 6 months of age, it is considered permanent.

AUTHOR DISCLOSURE Drs Kota, Kumar, and Ejaz have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The primary differential diagnosis of hyperglycemia in this age is type 1 diabetes, which usually results from autoimmune destruction of pancreatic islet cells. Absence of autoimmune markers suggests neonatal diabetes. Other possibilities include anatomic defects of pancreas and congenital syndromes such as immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, and Wollcott-Rallison syndrome.

IPEX syndrome is an X-linked condition caused by a mutation on the *FOXP3* gene. Clinical presentation includes early-onset insulin-dependent diabetes, dermatitis, enteropathy, failure to thrive, thyroiditis, hemolytic anemia, and thrombocytopenia. Wollcott-Rallison syndrome is a rare autosomal recessive disorder reported to be the most common cause of permanent neonatal diabetes in consanguineous families. It is caused by a mutation of the eukaryotic translation initiation factor 2-α kinase 3 (*EIF2AK3*). These patients present with growth failure, skeletal dysplasia, liver failure, exocrine pancreatic insufficiency, and neutropenia with recurrent infections.

Pancreatic islets consist of 4 types of cells: alpha cells secrete glucagon, beta cells secrete insulin, delta cells secrete somatostatin, and gamma cells secrete pancreatic polypeptide. Insulin secretion is regulated by the opening and closing of voltage-gated calcium channels and adenosine triphosphate (ATP)–sensitive potassium channels. These channels are embedded in the cell membrane of the beta cells.

The ATP-sensitive potassium channel (K_{ATP}) in beta cells of the pancreas is an octamer consisting of 4 subunits of the inward rectifying potassium channel 6.2 (Kir 6.2), encoded by the *KCNJ11* gene, surrounded by 4 regulatory subunits of sulfonylurea receptor 1 (SUR1), encoded by the *ABCC8* gene. These genes are located on chromosome 11. The opening and closing of these channels control the release of insulin from the beta cells.

About half of the cases of permanent diabetes have been associated with activating mutations of the Kir6.2 (KCNJ11) and SUR 1(ABCC8) subunits. Transient diabetes is usually caused by disturbances in the imprinted genes pleomorphic adenoma gene-like 1 (*PLAGL-1*) and hydatidiform mole-associated and imprinted transcript (*HYMAI*).

The affected infants are usually small for gestational age, reflecting in utero deficiency of insulin. Delay in diagnosis results in severe dehydration and diabetic ketoacidosis. Some infants have associated renal and cardiac abnormalities and may have coarse facial features. Severe mutations in *KCNJ11* have been associated with severe developmental delay, muscle weakness, and epilepsy, termed *DEND syndrome*.

This condition is caused by mutation of beta cell ATP-sensitive potassium channel, thus most of these patients can be treated with sulfonylureas. Transition to oral sulfonylureas is often successful in infants; however, patients with DEND syndrome usually need to continue to receive subcutaneous insulin.

Management

Maintaining appropriate glycemic control can be challenging in pediatric patients, especially in infants. Extreme fluctuations in the blood glucose levels can be associated with poor neurodevelopmental outcomes. Although these patients can be treated with diluted subcutaneous insulin injections, starting an insulin pump is a preferable option in infancy. The parents should receive nutrition counseling to understand the caloric requirement at this age group. Insulin requirements change frequently and periodic evaluations are necessary.

Many infants with identified *KCNJ11* mutations who were previously treated with insulin have successfully transitioned to oral sulfonylurea in recent years. Second-generation sulfonylureas such as glibenclamide and glyburide have shown promising results in achieving good glycemic control as well as reducing the incidence of neurologic symptoms. Reported side effects of sulfonylureas include hypoglycemia, nausea, abdominal discomfort, and transient diarrhea.

The current patient was discharged from the hospital with a combination regimen of long-acting insulin glargine and short-acting insulin lispro. He made a successful transition to sulfonylurea after a few months and continues to maintain good glycemic control and develop appropriately at the time of this writing.

Lessons for the Clinician

- Neonatal diabetes mellitus is a rare form of monogenic diabetes classified into temporary and permanent types. Infants are usually small for gestational age and may present with failure to thrive.
- Mutations causing permanent neonatal diabetes such as *Kir6.2* mutations have been associated with developmental delay and epilepsy and need close neurologic monitoring.
- Genetic testing plays a vital role in determining the type of diabetes and treatment options.

Note: This case is based on a presentation (poster #5166) by Drs Kota, Kumar and Ejaz at the ENDO 2019 Annual Meeting, New Orleans, LA, on March 24, 2019.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes, including genetic disorders and other clinical conditions, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the clinical and laboratory features and approach to therapy of neonatal hyperglycemia, including transient diabetes mellitus.

Suggested Readings

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Case 3: Poor Weight Gain and Severe Dehydration in a 3-month-old Infant

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Decreased Fetal Movement and Abnormal Fetal Heart Rate Monitoring

Caitlin MacGregor, MD,* Ian Grable, MD*
*Division of Maternal-Fetal Medicine, NorthShore University Health System/University of Chicago School of Medicine, Evanston, IL

ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

AUTHOR DISCLOSURE Drs MacGregor and Grable have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤–10 (–2.0 to –9.0)
Respiratory acidosis	<7.20	>60	Variable	≤–10
Metabolic acidosis	<7.20	<60	Variable	≥–10
Mixed acidosis	<7.20	>60	Variable	≥–10

Normal ranges from Obstet Gynecol Clin North Am. *1999;26:695.*

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

  Absent: Amplitude range is undetectable
  Minimal: Amplitude range is greater than undetectable to 5 beats/min
  Moderate: Amplitude range is 6–25 beats/min
  Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes

  – Normal: ≤5 contractions in 10 minutes
  – Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

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  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

History

A 27-year-old, gravida 2, para 0-0-1-0 woman at 34 3/7 weeks' gestation presented with decreased fetal movement. Her pregnancy was notable for an increased nuchal translucency of 3.3 mm on a first-trimester ultrasound scan with subsequent low-risk cell-free fetal DNA testing and a normal maternal serum α-fetoprotein level. Her obstetrical history included 1 first-trimester spontaneous abortion. Her medical history was significant for well-controlled chronic hypertension for which she is currently taking no medication. Her surgical and family history were not otherwise notable. She was taking low-dose aspirin daily and prenatal vitamins.

Upon presentation to triage, EFM showed a category 2 FHR tracing (Fig 1). The decision was made to admit her for further monitoring. A peripheral intravenous (IV) line was started, IV fluids were given, and laboratory testing was performed (including a complete blood cell count, type, and screen). Betamethasone was ordered for fetal lung maturity, given the concern for fetal well-being and a potential preterm delivery. Her cervical status was closed/long.

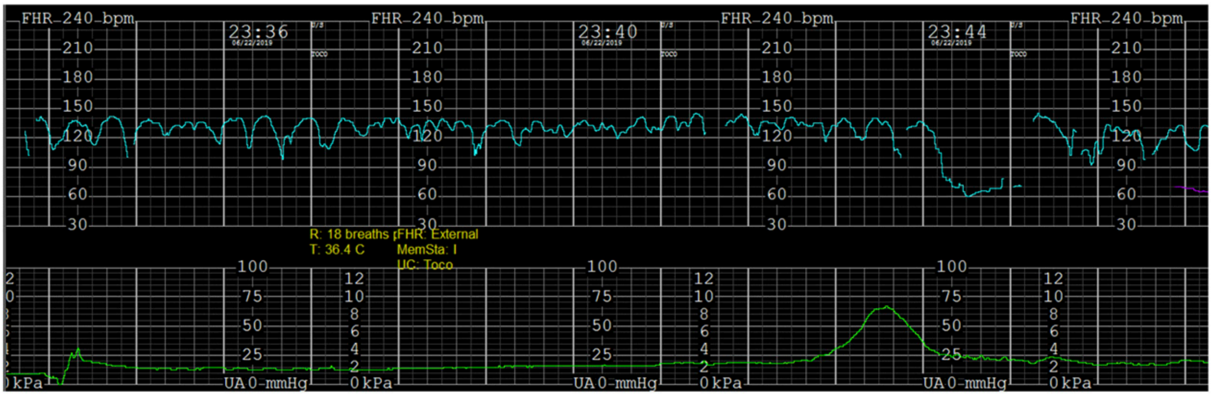

Figure 1. Electronic fetal monitoring strip 1.

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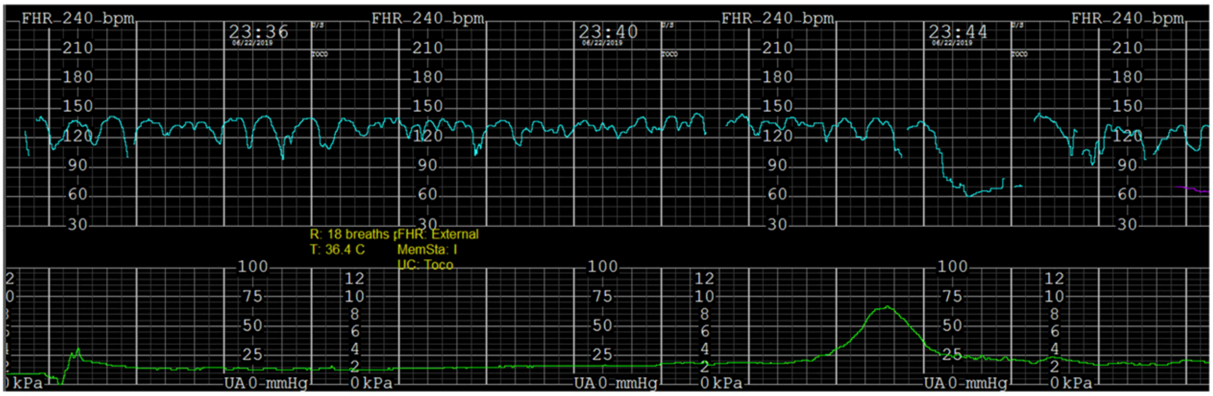

Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows (Fig 1):

- Baseline rate: 130 beats/min
- Variability: Moderate to marked
- Episodic pattern: Variable decelerations
- Periodic pattern: None
- Uterine contractions: Rare
- Interpretation: Category 2
- Differential diagnosis: Umbilical cord compression, uteroplacental insufficiency
- Action: Resuscitation with IV fluids, continued monitoring

She was moved from triage to the labor and delivery department. EFM demonstrated continued variable decelerations, and resuscitative measures with IV fluids were instituted (Fig 2).

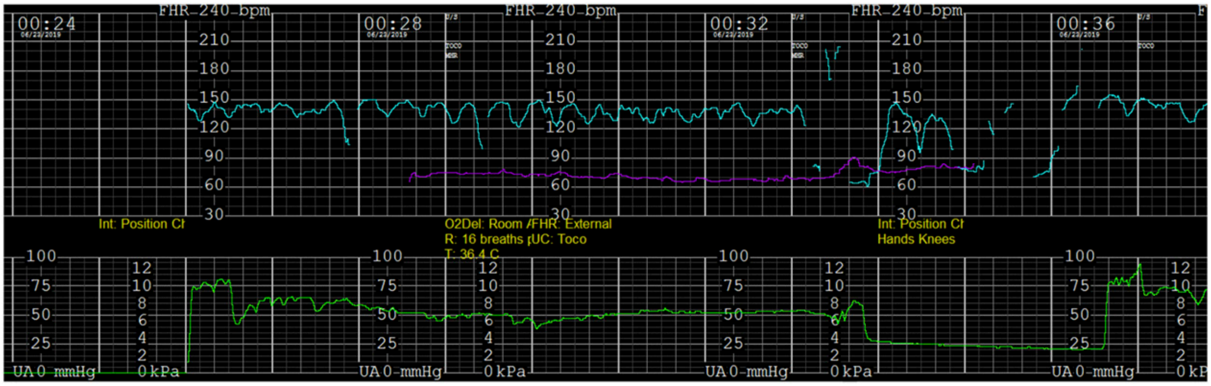

Figure 2. Electronic fetal monitoring strip 2.

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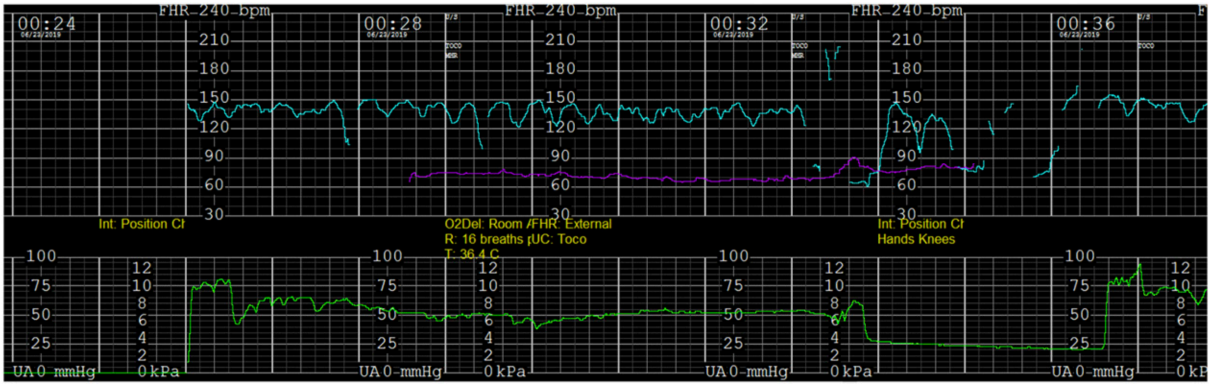

Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows (Fig 2):

- Baseline rate: 135 beats/min
- Variability: Moderate
- Episodic pattern: Variable decelerations
- Periodic pattern: None
- Decelerations: Variable
- Uterine contractions: None
- Interpretation: Category 2
- Differential diagnosis: Umbilical cord compression, uteroplacental insufficiency
- Action: Resuscitation with IV fluids, continued monitoring

Despite fluid resuscitation, a category 2 tracing persisted (Fig 3).

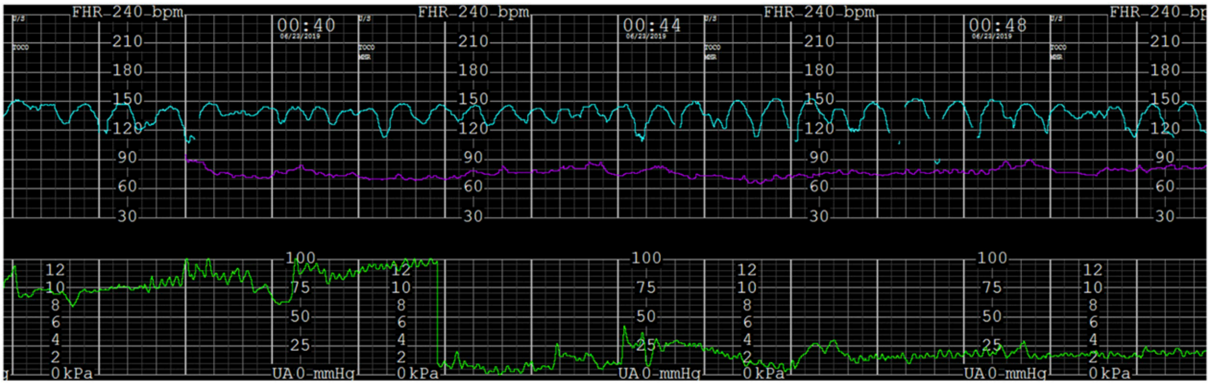

Figure 3. Electronic fetal monitoring strip 3.

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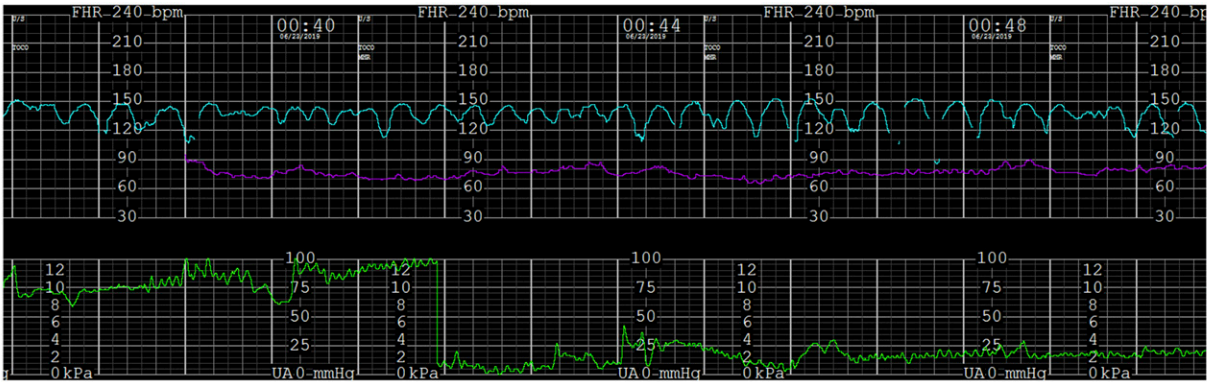

Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows (Fig 3):

- Baseline rate: 135 beats/min
- Variability: Moderate to marked
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category 2
- Differential diagnosis: Uteroplacental insufficiency, fetal anemia
- Action: Continued monitoring

Approximately 79 minutes after arrival at the hospital, the obstetrical team was called to the room for a prolonged deceleration (Fig 4). The patient was given supplemental oxygen, an IV fluid bolus, and repositioned. Her cervical status remained unchanged at closed/long. Ultrasonography performed at the bedside visually confirmed the prolonged fetal bradycardia. Emergent cesarean delivery was performed.

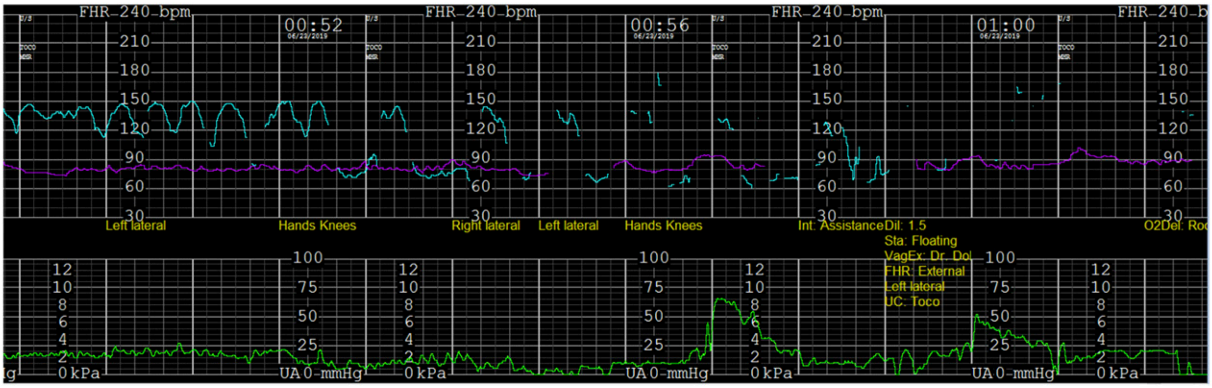

Figure 4. Electronic fetal monitoring strip 4.

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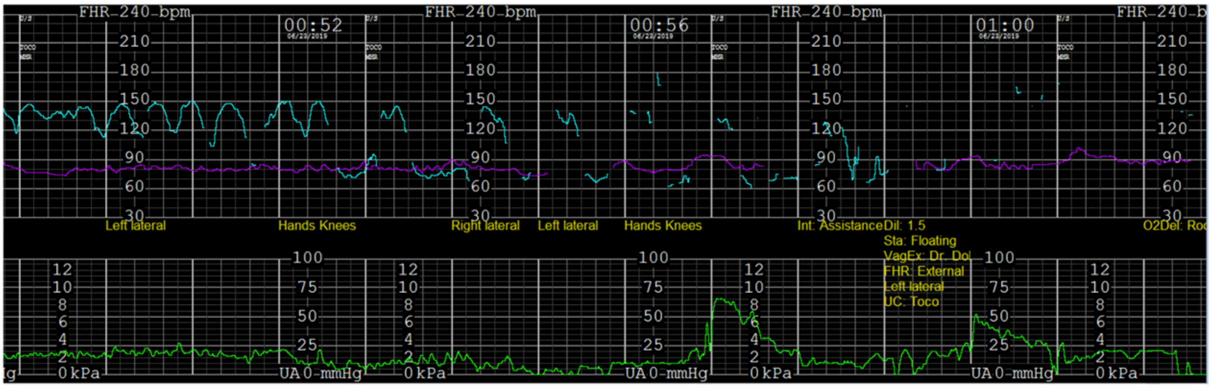

Figure 4. Electronic fetal monitoring strip 4.

Findings from EFM strip 4 are as follows (Fig 4):

- Baseline rate: 135 beats/min
- Variability: Marked
- Episodic pattern: Variable deceleration, prolonged bradycardia
- Periodic pattern: None
- Decelerations: Variable, then prolonged bradycardia
- Uterine contractions: None
- Interpretation: Category 2
- Differential diagnosis: Umbilical cord compression, abruption, fetal anemia
- Action: Resuscitative measures, emergent delivery via cesarean

Outcome

The patient initially presented to the labor and delivery department at 11:33 pm and was immediately placed on the EFM. Emergent cesarean delivery was decided at 12:58 am the following morning because of the prolonged bradycardia. The patient arrived in the operating room at 1:06 am, and a 2,710-g viable female infant was delivered at 1:13 am in an uncomplicated primary low transverse cesarean delivery (7 minutes after transfer to the operating room). The infant's Apgar scores were 2, 6, and 8 at 1, 5, and 10 minutes, respectively. Meconium-stained fluid was noted, but with no evidence of placental abruption at delivery. However, the infant was extremely pale. The neonatology team was present at the delivery. The umbilical artery cord blood gas measurements were as follows: pH 7.20, Pco_2 46 mm Hg (6.1 kPa), Po_2 55 mm Hg (7.3 kPa), and base excess −10. (Note: the umbilical venous cord blood gas could not be processed.) Placental pathology was benign with no evidence of abruption.

The neonate was admitted to the NICU for prematurity, severe anemia, and respiratory distress. Her initial vital signs demonstrated mildly decreased blood pressures and a normal heart rate. Her hemoglobin concentration immediately after birth was 4.1 g/dL (41 g/L; normal 14.2–22.1 g/dL [142–221 g/L]) and hematocrit was 12.7% (normal 45%–67%). The infant's reticulocyte count was 12.0% (normal 1.8%–4.6%) and the lactate level was 83.7 mg/dL (9.3 mmol/L; normal 6.3–18.9 mg/dL [0.7–2.1 mmol/L]). She received 30 mL/kg of packed red blood cells over a 10-hour period with hemoglobin improving to 13.3 g/dL (133 g/L) on day 2 after birth. Given the suspicion for a fetomaternal hemorrhage (FMH), a Kleihauer-Betke acid elution assay was performed on maternal blood, which showed a result of 5.20% (normal <0.10%). The infant initially required respiratory support with continuous positive airway pressure and was weaned to room air on day 4 after birth. She tolerated her feedings, and was discharged from the hospital on day 11 after birth.

DISCUSSION

Fetomaternal bleeding is the entry of fetal blood into the maternal circulation and occurs in most pregnancies without clinical significance. The frequency and volume of fetomaternal bleeding increases throughout gestation. (1) Spontaneous massive FMH is much less common. Although its true incidence is unknown, studies have estimated the frequency of FMH to be approximately 1 in 1,146 to 1 in 1,429 deliveries. (2)(3) Although the placenta is considered to be a barrier that separates the fetal and

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maternal circulations, small numbers of red blood cells pass between the pregnant woman and the fetus. (1)(4)(5) Disruption of the maternal-fetal barrier causes hemorrhage from the fetal circulation into the maternal circulation because fetal placental blood vessels have higher pressure than the intervillous space. (6)

Risk factors for FMH include motor vehicle accidents, maternal abdominal trauma, maternal falls, external cephalic version, amniocentesis, chorionic villous sampling, placental abruption, and placental anomalies. (5) However, the majority of cases occur spontaneously with no antecedent event. The most common presenting symptom of massive FMH is decreased or absent fetal movement (27% and 54%, respectively). (7)(8) In a series of 120 cases, the initial presenting symptom for FMH was neonatal anemia (35.0%). (8) A sinusoidal pattern on EFM is associated with fetal anemia, but it is uncommonly seen as the presenting symptom of massive FMH, occurring in only 1.7% of cases. (8) The classic sinusoidal pattern is a smooth, regular form of a sine wave occurring with a frequency of 2 to 5 cycles per minute and an amplitude range of 5 to 15 beats/min. A sinusoidal pattern can also be associated with acidosis and hypoxia. A nonreassuring FHR is the initial symptom in approximately 6.7% of patients. (8)

The 2 maternal tests available to estimate the volume of FMH are the Kleihauer-Betke acid elution assay and flow cytometry. (9) Both tests identify the amount of hemoglobin F (the predominant fetal hemoglobin) in the maternal circulation. Although flow cytometry has a faster turnaround than the Kleihauer-Betke assay, management decisions are typically made based on clinical presentation and examination.

In this case, decreased fetal movement was the initial presenting symptom of FMH. Although a category 2 FHR tracing was noted in this patient, the classic sinusoidal pattern was not. Prompt delivery and NICU care led to a good outcome for this infant. Antenatal diagnosis of massive FMH requires a high index of suspicion, given the nonspecific presenting signs. (10) Recurrent massive FMH in subsequent pregnancies has been described in case reports. (11) However, there is no evidence on which to base a recommendation for future pregnancies.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand the rationale, interpretation, and limitations of maternal detection of fetal movement, of the biophysical profile, the non-stress test, and the contraction stress test as means of assessing fetal well-being.
- Know how to assess fetal well-being during labor.
- Know the diagnosis and management of maternal/fetal blood loss such as placenta previa, placenta abruption, vasa previa, and maternal-fetal hemorrhage.

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NeoReviews 2020;21;e55
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Fetoscopic Myelomeningocele Repair

Stefanie Riddle, MD,*‡§ Jose L. Peiro, MD, PhD,*† Foong-Yen Lim, MD,*†
Paul S. Kingma, MD, PhD*‡§
*Cincinnati Fetal Center, Cincinnati, OH
†Division of Pediatric General, Thoracic, and Fetal Surgery, Cincinnati Children's Hospital, Cincinnati, OH
‡Division of Neonatology, Cincinnati Children's Hospital, Cincinnati, OH
§Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, OH

CASE PRESENTATION

A 34-year-old gravida 6, para 2-0-3-2 pregnant woman was referred to the Cincinnati Fetal Center with a diagnosis of fetal lumbosacral myelomeningocele (MMC). Her medical history was significant for polycystic ovarian syndrome, migraine headaches, seasonal allergies, and anxiety. She had a surgical history of wisdom teeth extraction and 2 prior cesarean sections. She was taking prenatal vitamins and using vaginal progesterone for an obstetrical history of 3 early first-trimester spontaneous abortions. She had no family history of neural tube defects, but 1 child with Asperger syndrome and sensory processing disorder and 1 child with speech delay. Prenatal laboratory testing was unremarkable. Imaging at the referring obstetrician's office was significant for an L3 lesion with a lemon-shaped calvarium, findings of Chiari II malformation in the posterior fossa, and lateral ventricular enlargement with a dangling choroid. Amniocentesis performed by the referring provider showed a normal female karyotype and microarray.

She was referred to our center at 23 5/7 weeks' gestation, with imaging and multidisciplinary team meeting at 24 6/7 weeks' gestation. The following results were obtained:

- Fetal echocardiography showed normal cardiac anatomy and function.
- Fetal magnetic resonance imaging (MRI) revealed colpocephalic configuration of the lateral ventricles, measuring 11 mm bilaterally, a normal third ventricle and effacement of the fourth ventricle. There were also findings of grade 3 Chiari malformation, including a small posterior fossa with herniation of cerebellar tissue into the midcervical spine, which partially wraps around the brainstem (Fig 1, A). An open spinal dysraphism of the lumbar spine was seen, measuring approximately 2.7×1.2 cm at the skin surface. No sac was identified, which suggested a diagnosis of myeloschisis.
- Ultrasonography showed splaying of vertebral elements at L3, normal lower extremity positioning (no clubfoot) and motion, a cervical length of 3.5 cm, and no other fetal anomalies.

EXPERT OPINION

At our center, families with a fetal diagnosis of MMC undergo a combined multidisciplinary counseling session that includes maternal-fetal medicine, fetal

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ABBREVIATIONS

CSF	cerebrospinal fluid
MMC	myelomeningocele
MRI	magnetic resonance imaging
VP	ventriculoperitoneal

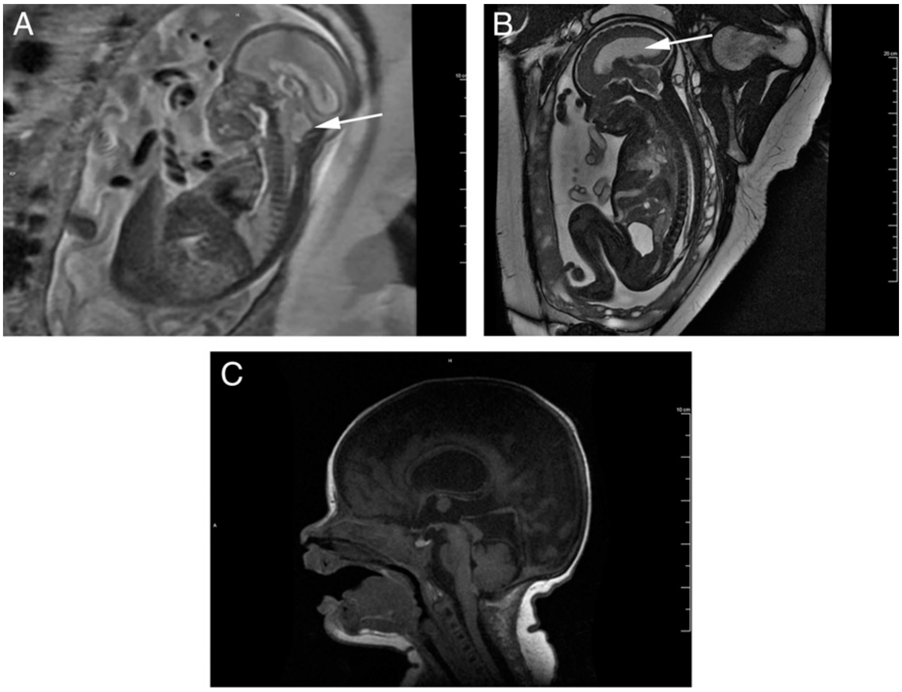

Figure 1. A. Prerepair fetal magnetic resonance imaging (MRI) findings, arrow indicates hindbrain herniation. B. Postrepair fetal MRI, arrow indicates ventriculomegaly. C. Postnatal MRI.

surgery, neonatology, neurosurgery, social work, genetic counseling, and developmental pediatrics. They also meet with our center's Spina Bifida Clinic staff regarding outpatient management after NICU discharge. In the first phase of counseling, families learn about the traditional standard-of-care approach for a pregnancy with a fetal neural tube defect, including antenatal monitoring, and the expected course of neonatal care, including postnatal MMC repair.

As part of their visit to the Fetal Center, families receive extensive counseling about the prognosis for infants with MMC. They learn that live-born infants with MMC have a mortality rate of 10%, and survivors experience major disability owing to the spinal cord injury, including lower limb, bowel, and bladder dysfunction. (1) Nearly all infants born with MMC will have Chiari II malformation (displacement of the medulla, fourth ventricle, and cerebellum into the spinal canal), and depending on the severity of hindbrain herniation, this malformation can cause further neurologic defects (motor dysfunction, cranial nerve injury, and cognitive impairment). The Chiari malformation is also associated with the development of hydrocephalus; thus, ~80% of infants with MMC will require diversion of cerebrospinal fluid (CSF) from the brain into the peritoneal cavity with a ventriculoperitoneal (VP) shunt. Most infants will experience shunt complications and require other surgeries for shunt revision in the first decades of life.

Following this initial educational meeting, if patients are found to be candidates for fetal repair, they undergo 2 additional phases of multidisciplinary counseling regarding the risks, benefits, and alternatives to fetal surgery. Patients must meet all inclusion criteria for fetal repair with no exclusion criteria (Table). The second phase of counseling with clinicians in maternal-fetal medicine, fetal surgery, and neonatology centers around the technical aspects of fetal MMC repair, published literature including risks and benefits of the procedure, center-specific outcomes, expected postoperative monitoring practices, and neonatal implications of fetal repair. If they continue to express interest in fetal repair, they return for a third phase of counseling that also includes an anesthesia consultation, preoperative planning, and review of consent documents. Part of this phase 2 and 3 counseling also involves discussion of the 2 approaches or modalities offered at our center for fetal MMC repair—open and fetoscopic. Open repair has been offered at our center since 2011; fetoscopic repair began in 2015.

OUTCOME

The patient was found to be a candidate for fetal surgery, and after receiving information on both the open fetal MMC repair (Fig 2) and fetoscopic MMC repair, she and her husband consented to the procedure and elected to proceed with the fetoscopic approach. This was performed at 25 6/7

TABLE. **Inclusion and Exclusion Criteria for Open and Fetoscopic Repair**

INCLUSION CRITERIA	EXCLUSION CRITERIA
• The fetal lesion confirmed at level T1 through S1 and there is hindbrain herniation confirmed on MRI.	• Significant fetal anomalies identified unrelated to the MMC.
• Maternal age >18 years	• Kyphosis in the fetus of greater than 30 degrees.
• The gestational age 19 0/7 weeks to 25 6/7 at the time of prenatal surgery	• History of incompetent cervix
• Normal karyotype	• Cerclage in place.
• Normal fetal echocardiogram	• BMI is >35 kg/m^2
• Singleton pregnancy	• Maternal history of previous hysterotomy in the active segment of the uterus • History of HIV, hepatitis B, or hepatitis C • Maternal history of uterine anomalies • Maternal medical conditions that contraindicate abdominal surgery or general anesthesia • Normal psychosocial evaluation results, and availability of support person for the remainder of pregnancy

BMI=body mass index; MMC=myelomeningocele; MRI=magnetic resonance imaging.

weeks' gestation. A midline maternal laparotomy was performed for uterine exposure and a fetoscopic approach with 3 minicannulas (2- and 3-mm diameter) was used for repair. Fetal intramuscular injection with an anesthetic cocktail (fentanyl, atropine, vecuronium) was given. Maternal anesthesia was maintained with inhalational agents for uterine relaxation per standard protocols. Using ultrasound guidance, fetal repositioning was performed. Amnioinsufflation was performed with warm humidified carbon dioxide up to 10 mm Hg. Once the cannulas were introduced, the placode was identified and carefully released into the spinal canal (Fig 3). The fascia and skin around the defect were freed, and a patch was introduced over the placode as a dural substitute. This patch was attached to the fascia with 4-0 barbed absorbable sutures. The skin was primarily closed using running continuous 3-0 nonabsorbable barbed sutures with the wound closure device. Intra-amniotic antibiotic (nafcillin) and warm lactated Ringer fluid were introduced after carbon dioxide was removed. Previously, introducer sites were closed under direct visualization to approximate the membrane orifice edges. The midline maternal laparotomy was then closed with usual methods. Fetal echocardiography was performed throughout the procedure, with no fetal distress or Doppler changes noted.

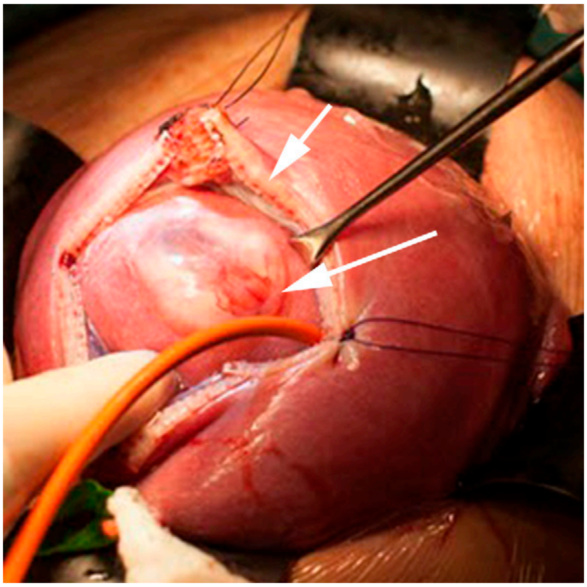

Figure 2. Open fetal repair of a myelomeningocele (MMC). View of exposed and externalized uterus that has been opened to reveal the MMC on back of fetus. Short arrow indicates edge of opening in uterus, long arrow indicates edge of MMC placode on back of fetus.

The patient was monitored in house per standard guidelines until postoperative day 6. Initial pain control was managed with an epidural catheter, followed by transition

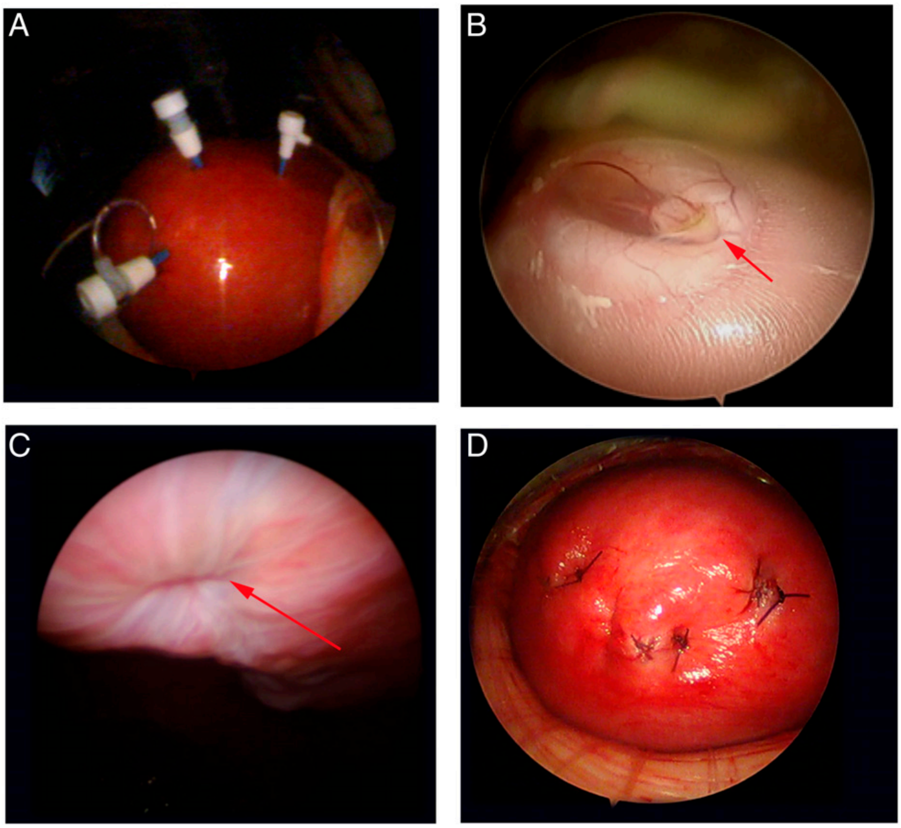

Figure 3. Fetoscopic repair of a myelomeningocele (MMC). A. External view of uterus and placement of cannulas. B. Fetoscopic view of unrepaired MMC, arrow indicates back of fetus and edge of MMC placode. C. Internal view of closed canulla site (arrow) on uterine wall. D. External view of completed uterine closure.

to oral narcotics. She received antenatal corticosteroids on postoperative day 0 to 1 because of contractions, which resolved with tocolysis per standard protocols. She was discharged with treatment with nifedipine 20 mg every 6 hours. A second fetal MRI was performed at 29 3/7 weeks' gestation. The expected postrepair changes were visualized, including significant improvement of the Chiari II malformation from grade 3 to grade 1 (Fig 1B). Lateral ventriculomegaly was present, which was measured 18 mm in maximal dimension. Follow-up ultrasonography revealed normal amniotic fluid volume and fetal growth, but chorioamnion separation developed at 31 weeks' gestation, as well as progression of ventriculomegaly (the maximum ventricular measurement was 22.5 mm at 33 weeks' gestation).

The patient presented at 33 2/7 weeks' gestation with vaginal bleeding and loss of fluid, and she was confirmed to have premature preterm rupture of membranes. She was admitted and received a second course of betamethasone and latency antibiotics. On hospital day 3, she developed worsening vaginal bleeding concerning for possible abruption, and was taken for cesarean delivery.

NEONATAL COURSE

A 2,311-g viable female neonate was delivered via repeat cesarean section at 33 5/7 weeks' gestation. Apgar scores were 9 at 1 and 5 minutes, and the infant was admitted to the NICU in room air. The infant was positioned prone until neurosurgical evaluation of the repair site. Her initial physical examination findings were significant for a slight decrease in lower extremity tone and muscle mass, but spontaneous movement was noted in both legs and feet. Upon inspection of the fetal MMC repair site, there was a small (2–3 mm in diameter) area where a gap was noted between the healing skin edges. The underlying dural patch was visible but no CSF leak was evident.

An infectious evaluation for rupture of membranes was negative, and the infant received broad-spectrum antibiotics for 48 hours. Oral/nasogastric feedings were started on the first day after birth, and she advanced to full enteral feedings by 4 days of age. She was able to transition to full oral feedings at 35 days of age. The infant was voiding and passing stools spontaneously but did receive regular bladder catheterization to support bladder emptying. Of note, the infant developed multiple episodes of supraventricular tachycardia and was ultimately diagnosed with Wolff-Parkinson-White syndrome. Echocardiographic findings were normal. She was unresponsive to treatment with propranolol and flecainide, but her condition resolved with transition to sotalol.

Initial head ultrasonography showed lateral ventricular sizes of 20 mm and 18 mm on the left and right, respectively. Serial weekly imaging showed minimal progression of ventricular size, and no neurosurgical interventions were required for hydrocephalus. The MRI at 3 weeks of age (Fig 1C) showed mild-to-moderate ventriculomegaly, mild tectal beaking, and superior tenting of the tentorium cerebelli. There was no significant crowding of structures in the posterior fossa and no herniation of cerebellar tissue through the tentorium or foramen magnum; these findings were consistent with improved Chiari II malformation compared with the preoperative state.

The infant was discharged from the NICU at 38 days of age, at 38 4/7 weeks' postmenstrual gestation. At the time of discharge, the infant's weight was 3.310 kg (about 1 kg above birth weight) and she was taking full volume oral feedings. The surgical site was completely healed with no signs of underlying pseudomeningocele. Spontaneous, symmetric movement was noted in all extremities including movement of the hip, knee, and ankle. The rest of the neurologic examination findings were normal for the infant's age. The infant was voiding and passing stools spontaneously but still receiving bladder catheterizations to ensure complete bladder emptying and avoid risk of urinary tract infection.

DISCUSSION

Spina bifida is caused by the failure of embryonic neural tube closure and has an incidence of approximately 3.7 in 10,000 births. Spina bifida is a broad term that includes multiple lesions; MMC is the most common and severe type of spina bifida that involves herniation of the spinal cord and meninges. Patients with MMC have variable amounts of injury to the spinal cord, which is a result of exposure to amniotic fluid, as well as from incomplete development and maturation of neural pathways. Persistent leakage of CSF from the lesion leads to collapse of the posterior fossa and generates encephalic changes, including Chiari malformation. This can result in multiple morbidities, including hydrocephalus, complications of Chiari II malformation, paralysis, lower extremity malformations, and bladder and bowel dysfunction.

Before the introduction of fetal repair of neural tube defects, fetal surgery was limited to diagnoses that were considered fatal for the fetus or infant without intervention. However, a growing body of data in the early 1990s suggested that the neurologic outcome of patients with spina bifida was directly related to progressive injury resulting from exposure of the spinal cord during pregnancy. At the same time, multiple groups described successful fetal repair of MMC and improved outcome in animal models. In 1999, Bruner et al reported their results with over 60 patients who underwent open fetal MMC repair at Vanderbilt University. (2) When these cases were compared to control patients who were treated during the same period, their data suggested that open fetal MMC repair was associated with a significant reduction in the need for VP shunts and a significant increase in the risk of prematurity. Reports from Children's Hospital of Philadelphia during the same period corroborated these findings. (3)(4) Two years later, the prospective randomized trial of prenatal versus postnatal repair of MMC (the MOMS trial) was initiated. (5) The MOMS trial demonstrated a significant reduction in the need for VP shunt in the fetal repair group (40% VP shunt rate in the fetal repair group vs 82% in the postnatal repair group, $P<.001$) and an improved composite score for mental development and motor function at age 30 months in the fetal repair group ($P=.007$), but the the risk of preterm delivery and uterine dehiscence in the fetal repair group was also increased. The average gestational age at delivery in the fetal repair group was 34 weeks, with 10% delivered before 30 weeks' gestation. In comparison, the postnatal repair group had an average of 37 weeks' gestation, with no infants delivered before 30 weeks' gestation. Long-term outcomes from the randomized trial have not yet been published.

Following the MOMS trial, several centers began offering fetal repair of MMC. Despite the enthusiasm for fetal MMC repair, the wisdom of this approach is still uncertain. Open fetal repair of MMC was a landmark event in fetal medicine, but clearly there is room for improvement with this procedure. Over the last 4 years, our center and others have pioneered the technique of fetoscopic repair. (6)(7) By avoiding a large uterine hysterotomy, there are many potential benefits to the pregnant woman and fetus with this type of repair, including the possibility of vaginal delivery in the index and subsequent pregnancies. In the history of fetal surgery, the balance between maternal risk and fetal benefit has always been a large part of the ethical discussion. By minimizing maternal risk in this and subsequent pregnancies with a minimally invasive technique, the potential to optimize fetal benefit makes the fetoscopic technique potentially attractive to both providers and patients. Despite the improved risk/benefit profile, risks within the pregnancy continue to exist. As seen in this case, there is a risk of preterm rupture of membranes, preterm labor, and preterm delivery. While avoidance of a large hysterotomy allows more conservative management of these issues, the risk of preterm delivery with this procedure remains. More and more fetal centers are implementing a minimally invasive approach for the prenatal repair of MMC; some centers, including ours, recently created an international consortium and registry that may help to elucidate the efficacy of this new approach. Ultimately, fetoscopic MMC repair will require an appropriate evidence-based analysis demonstrating surgical efficacy (ie, watertight closure of the spinal defect) with similar or reduced maternal and fetal risks before widespread use can be adopted.

In summary, MMC is a serious and relatively common congenital defect that results from failure of the neural tube to close during fetal development. Exposure of the spinal cord to amniotic fluid causes damage to the spinal cord and incomplete development of the neural pathways. Further injury results from the persistent leakage of CSF from the spinal lesion and subsequent Chiari malformation and hydrocephalus. Ultimately, patients with MMC face higher mortality rates and multiple lifelong morbidities, including paralysis, lower extremity malformations, bladder and bowel dysfunction, hydrocephalus, and complications of Chiari malformation. The MOMS study demonstrated that open fetal repair of MMC improves the neurologic outcome of these patients; however, this improved neurologic function comes with the cost of greater maternal risks and increased risks associated with premature birth. Recent advances in fetal MMC repair using the fetoscopic approach demonstrated in the current case may offer similar improvements in neurologic function while also significantly reducing risks to the pregnant woman and fetus.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how specific fetal diagnoses, such as airway abnormalities, abdominal wall defects, myelomeningocele, or severe hydrocephalus might alter prenatal care and intrapartum management (eg, fetal intervention "Exit" strategy).
- Know the clinical and imaging findings, treatment, and outcome of myelomeningocele and encephalocele.

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ANSWER KEY FOR JANUARY 2020 NEOREVIEWS

Glucose Homeostasis in Newborns: An Endocrinology Perspective: 1. C; 2. B; 3. D; 4. A; 5. E.

Thyroid Function During the Fetal and Neonatal Periods: 1. C; 2. C; 3. A; 4. B; 5. D.

Complex Fetal Care Cases: Fetoscopic Myelomeningocele Repair

Stefanie Riddle, Jose L. Peiro, Foong-Yen Lim and Paul S. Kingma

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MOC

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Visual Diagnosis

An Unexpected Cranial Ultrasound Image

Catarina Ferraz Liz, MD,* Ana Novo, MD,† Marta Nascimento, MD,† José Eduardo Alves, MD,‡ Simão Frutuoso, MD,† Carmen Carvalho, MD†

**Pediatrics Department, Centro Hospitalar Tâmega e Sousa, Penafiel, Portugal*
†Neonatal Intensive Care Unit, Centro Materno Infantil do Norte, Porto, Portugal
‡Department of Neuroradiology, Centro Hospitalar Universitário do Porto, Porto, Portugal

THE CASE

A 13-day-old infant born at 39 weeks' gestation presents to the outpatient clinic with a previously diagnosed cephalohematoma that was increasing in size. Head ultrasonography showed an unexpected finding (Fig 1).

Prenatal and Birth Histories

- Born to a 34-year-old (gravida 1, para 1) white woman
- Uneventful pregnancy with unremarkable findings on prenatal laboratory screening and serial ultrasonography
- Estimated gestational age: 39 weeks
- Vaginal delivery assisted by vacuum extraction; rupture of amniotic membranes 2 hours before delivery, with clear amniotic fluid
- Prenatal maternal laboratory findings: HBsAg negative, HIV negative, VDRL negative, group B *Streptococcus* negative
- Apgar scores: 7, 10, and 10 at 1, 5, and 10 minutes, respectively
- Birthweight: 2,790 g (16th percentile); head circumference: 34 cm (44th percentile); length: 49.5 cm (42th percentile)
- Because of initial ineffective respiratory movements, positive pressure was applied via facemask for 30 seconds, with good response

Presentation

At 24 hours of age, the infant was found to have a moderate cephalohematoma in the right parieto-occipital region resulting from vacuum extraction. No other

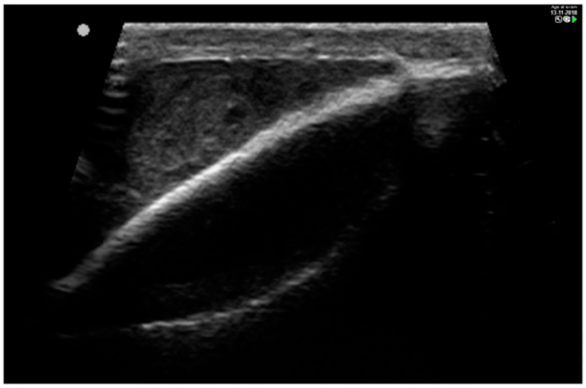

Figure 1. Hypoechoic image in the pericerebral space.

AUTHOR DISCLOSURE Drs Ferraz Liz, Novo, Nascimento, Alves, Frutuoso, and Carvalho have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

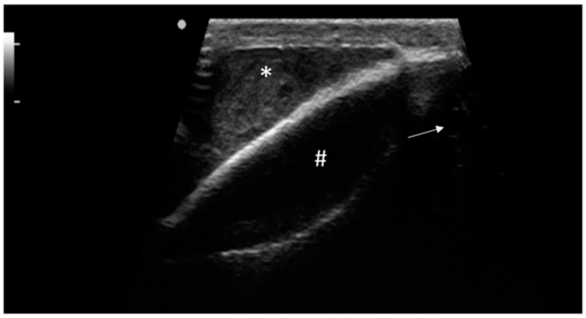

Figure 2. Hypoechoic image in the pericerebral space. Arrow=brain, falx cerebri; *=cephalohematoma, #=mirror image in the pericerebral space.

abnormalities were found on physical examination. The infant was discharged from the hospital at 48 hours of age. At 13 days of age, he was brought to the outpatient clinic with the cephalohematoma increasing in size. The parents denied a history of fever, irritability, vomiting, or other symptoms. The newborn was breastfed, with a weight gain of 35 g/day. Cranial ultrasonography performed in the outpatient clinic was suspicious for epidural hematoma and the infant was immediately taken to the emergency department.

PROGRESSION

Vital Signs

- Heart rate: 123 beats/min
- Respiratory rate: 32 breaths/min
- Blood pressure: 70/38 mm Hg
- Oxygen saturation: 98% (in room air)
- Temperature: 36.2°C (97.2°F)

Physical Examination (13 Days After Birth)

- Weight 3,245 g (36th percentile); head circumference: 37 cm (80th percentile); length 50 cm (58th percentile)
- Head: Soft and flat fontanelles; moderate cephalohematoma, 4×3 cm, in the parieto-occipital region, not crossing suture lines, no transillumination or abnormalities of overlying skin
- Oral: Normal sucking and rooting reflex
- Lungs: No signs of respiratory distress; breaths sounds audible and symmetrical
- Cardiovascular: Regular rate and rhythm; no murmurs or gallops
- Abdomen: Soft, nondistended; bowel sounds present; no hepatosplenomegaly
- Genitourinary: Normal term male genitalia, patent anus
- Skin: Pink; no icterus or erythema
- Neurologic: Active, alert; symmetric movements of all 4 extremities; normal strength and tone; symmetric Moro reflex

No laboratory studies were performed. Head ultrasonography was performed in the emergency department (Fig 1).

DIFFERENTIAL DIAGNOSIS

- Cephalohematoma with mirror image artifact
- Epidural hematoma
- Subdural hematoma
- Subgaleal hematoma

ACTUAL DIAGNOSIS

Cephalohematoma with mirror image artifact.

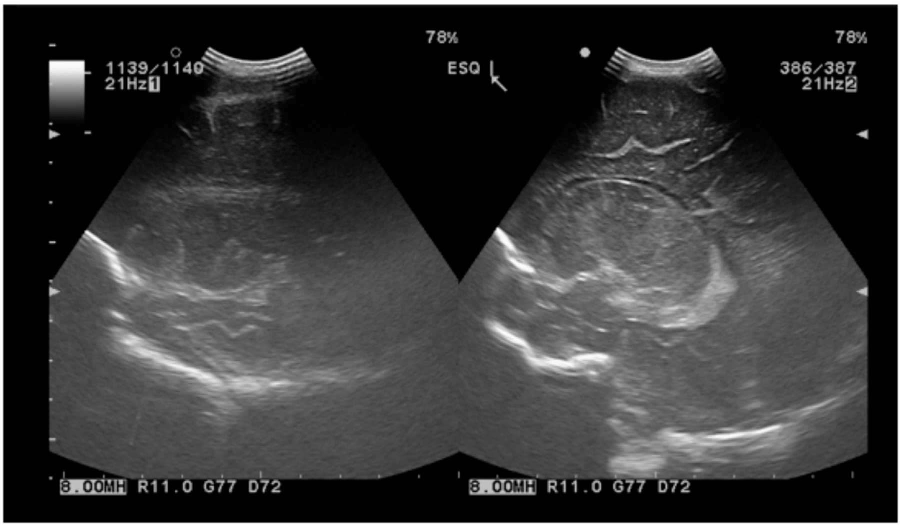

Figure 3. Left-sided sagittal views showing normal ventricular size, without sulcal effacement or parenchymal deformation (expected secondary signs of intracranial mass lesions).

Ultrasonography performed at 13 days of age showed a right parietal cephalohematoma associated with a hypoechoic image in the pericerebral space, underneath the cephalohematoma, with no mass effect: no sulcal effacement, parenchymal deformation, or shift of midline structures (as would be expected if there were a real pericerebral collection) (Figs 2 and 3). Compression of the hypoechoic structure decreased the size of the image, which was consistent with a mirror image artifact.

The patient was discharged, and follow-up head ultrasonography performed within a week re-demonstrated the mirror image artifact without additional findings. The patient remained clinically asymptomatic with progressive resolution of the cephalohematoma.

WHAT THE EXPERTS SAY

Mirror artifact images in ultrasonography have been described when the ultrasound beam strikes an echogenic structure obliquely. This event creates a refraction artifact that can cause duplication of the image or enlargement of its size. One of the methods used to verify these artifacts in cephalohematomas includes the compression of the lesion, with the probe leading to a reduction of the mirror image. Another method described is the use of Doppler ultrasonography to differentiate the structure from an epidural hematoma. In the case of a cephalohematoma, Doppler ultrasonography will reveal a normal parenchymal vascularity with blood vessels crossing the space.

The infant described here had a cephalohematoma at birth and normal neurologic examination findings. Ultrasonography showed an anechoic image resembling an epidural hematoma; however, when higher pressure was applied with the probe over the cephalohematoma, the hypoechoic image presented a similar reduction pointing to a mirror image. Subgaleal, subdural, or epidural collections usually present with clinical instability such as vomiting, seizures, or bulging fontanelle, mainly after significant trauma. The combination of clinical and ultrasonographic features suggested that the anechoic image was most likely an ultrasound imaging artifact related to the overlying cephalohematoma. Cephalohematomas are usually smaller at birth, increasing in the following days because of the slow subperiosteal bleeding. Cephalohematomas resolve spontaneously over 2 to 3 weeks; as the blood starts to be reabsorbed, the hematoma may appear firmer due to calcification.

SUMMARY

- Head ultrasonography is an essential noninvasive diagnostic imaging technique in the newborn, providing valuable information for the diagnosis and management of brain lesions or intracranial collections.
- Mirror images may occur during ultrasonography, leading to a misdiagnosis.
- Clinicians should be aware of these artifacts to avoid parental anxiety or unnecessary additional imaging.
- Clinical examination must be taken into account for the correct interpretation and identification of artifacts seen on ultrasonography.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the indications for and limitations of various neuroimaging studies and be able to recognize normal and abnormal structures and changes during development and growth.
- Know the diagnostic, clinical, and imaging features of extracranial hemorrhage, including cephalohematoma and subgaleal hemorrhage.
- Know the management, complications, and outcomes of extracranial hemorrhage, including cephalohematoma and subgaleal hemorrhage.

Suggested Readings

Amosa Delgado M, Hernandez Garcia B, Ruiz Gines JA, Alvarez Salgado JA. False epidural hematoma in a neonatal ultrasound [in Spanish]. *An Pediatr (Barc)*. 2014;80(6):405–406

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Answer Key appears on page e149.

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Educational Perspectives: Palliative Care Education in Neonatal-Perinatal Medicine Fellowship

Katie R. Forman, DO,* Alecia Thompson-Branch, MD*

*Department of Pediatrics, Albert Einstein College of Medicine, Children's Hospital of Montefiore, Bronx, NY

Education Gaps

1. Opportunities for providing comprehensive palliative care may be missed in the NICU, limiting trainees' ability to learn the art of palliative care.
2. Neonatal-perinatal trainees may lack opportunities for formal training in how to provide palliative care.

Abstract

The neonatal period from birth to less than or equal to 28 days is one of increased risk of death. Congenital anomalies and prematurity are 2 of the most common risk factors for death at this early age. Many of these neonates will die in an intensive care unit, some with full resuscitative efforts being undertaken despite the understanding that these actions are highly unlikely to yield an outcome different from death. Palliative care allows curative therapies to be provided alongside supportive techniques such as enhanced family communication, attention to spirituality and the psychosocial health of the family, management of symptoms other than those specific to the underlying disease process, and enhancing comfort. The American Academy of Pediatrics has set forth recommendations related to pediatric palliative care for the various pediatric subspecialties; however, much of the focus is on disease processes and curing or mitigating various illnesses. Given the high preponderance of death in the neonatal period, neonatal-perinatal medicine training programs should be tasked with generating formal palliative care training. Such training should be geared to providing better care for neonatal patients with a life-limiting or life-altering illness, and better equipping future neonatologists with the tools needed to provide truly comprehensive care for their sickest patients at risk for death and disability. This article serves to review the concept of palliative care in neonates, discuss the paucity of formal education in palliative care, explore the general trend in palliative care education, review various ways in which palliative care education can be formalized, and define metrics of a successful educational program.

AUTHOR DISCLOSURE Drs Forman and Thompson-Branch have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After reading this article, readers should be able to:

1. Illustrate how exposure to formal palliative care education may enhance care of neonatal patients undergoing intensive care.
2. Share an example of a palliative care curriculum for neonatal-perinatal medicine fellows to illustrate how care for patients in the NICU can be augmented by palliative care education.
3. Illustrate how different teaching modalities can be used to educate neonatal-perinatal medicine fellows on the concepts of palliative care.
4. Review methods of evaluating a palliative care education program for NICU fellows.

INTRODUCTION

Palliative care provides comprehensive care for patients at risk for death or serious morbidity and can be used early in the disease trajectory concurrently with curative therapies. Palliative interventions neither prevent nor hasten death, but rather focus on augmenting the quality of life of patients who are imminently dying or those who have a life-threatening condition that significantly increases their risk of death. Using a team approach, careful assessment and attention are paid to the management of distressing symptoms, and support is provided to the patient and family with a focus on spirituality and psychosocial well-being. Bereavement support is an additional feature of optimal palliative care. (1) The term "palliative care" is often used synonymously with "end-of-life" care. The former term is comprehensive and refers to the broader scope of care for severely ill and dying patients. It encompasses a range of therapies and systems of supportive care for patients and families and is not specific to care at the end of life or a terminal illness. Table 1 describes the National Consensus Project's 8 domains of palliative care. (2)

Palliative care may be used in the NICU for a variety of patient subsets. Expectant couples may have to cope with advanced notice of a life-limiting illness and utilize palliative care services to plan the birth of the child and decide if additional medical services or a trial of therapy is warranted. Other families may have been undergoing a heretofore normal pregnancy, and in a very short time frame are faced with the birth of a severely ill or dying neonate. For each of these types of patients and their families, palliative care can confer a benefit. Given the paucity of board-certified pediatric palliative care physicians, neonatologists can improve the care provided to very ill and dying newborns by acquiring the skills necessary to enhance communication, manage distressing symptoms, and address spiritual and psychosocial concerns that affect care. (3) In a qualitative study of 10 parents facing end-of-life care for their infant in the NICU, 6 received a palliative care consultation. It was found that while parents were initially resistant to the inclusion of a palliative care team near the end of life, all 6 parents ultimately went on to value the extra layer of support. (4)

PALLIATIVE CARE EDUCATION

As physicians we are often focused on healing and curing our patients knowing that a portion of our patient populations will die despite our best efforts or live with extreme morbidity. This knowledge is humbling and calls for increased need for humanism in medicine. Many physicians will have to care for patients who are currently dying or at high risk, and it behooves us to have the skills to fully support this segment of our patient population. Exposure to the specialty of palliative care during medical school is limited. Medical school educators recognize the paucity of palliative care education and are starting to enhance palliative care education for the next generation of physicians. A study by Sullivan and colleagues in 2004 evaluated a cohort of national medical education deans' perceptions of end-of-life care education in medical schools. (5) They concluded that most deans felt that end-of-life care was important and that the time currently allocated to palliative care in their curriculum was insufficient. Although a majority of respondents did not support including required courses focusing on end-of-life care, they were in favor of integrating end-of-life care into existing courses or clerkships.

Medical school educators have experimented with curricula developed to enhance palliative care education for medical

TABLE 1. **National Consensus Project Clinical Practice Guideline for Quality Palliative Care: 8 Domains of Palliative Care and Alignment of Palliative Care Teaching Modules Along These Domains**

PALLIATIVE CARE DOMAIN	FOCUS	NEONATAL-PERINATAL PALLIATIVE CARE TEACHING MODULE/LECTURE
Structure and processes	Interdisciplinary, patient- and family-centered care	Practical aspects of the NICU death AND establishing goals of care/antenatal consultations for prenatally diagnosed fetal anomalies
Physical	Assessment, care planning, and treatment of physical symptoms	Physiology of dying AND practical aspects of the NICU death
Psychological and psychiatric aspects	Processes for systematically assessing and addressing contextual psychological and psychiatric aspects to care	Practical aspects of the NICU death AND perinatal bereavement and grief; using child life tools in providing palliative care
Social	Assess and address social support needs of the patient and family	Perinatal bereavement and grief; using child life tools in providing palliative care
Spiritual, religious, and existential	Supporting and screening for unmet spiritual, religious, and existential concerns	Spirituality, religion, and cultural practices in providing palliative care AND physician self-recognition of internal bias and its impact on medical care; resiliency tools for care providers and how to avoid being a second victim
Cultural	Mindfulness of how culture affects palliative care delivery and the experience of the family	Spirituality, religion, and cultural practices in providing palliative care AND physician self-recognition of internal bias and its impact on medical care; resiliency tools for care providers and how to avoid being a second victim
Care of patients nearing and at the end-of-life	Symptoms and scenarios common in dying patients	Physiology of dying AND spirituality, religion, and cultural practices in providing palliative care AND perinatal bereavement and grief; using child life tools in providing palliative care
Ethical and legal	Advanced care planning, regulatory and legal concerns	Redirection of medical care, advanced directives, New York State laws pertaining to palliative care, and principles of informed consent and shared decision-making AND establishing goals of care/antenatal consultations for prenatally diagnosed fetal anomalies

students. One such study in 2014 assessed data collected from fourth-year medical students at 62 medical schools in the United States. The authors strove to identify the determinants of students' perceived preparation for providing palliative care, the quality of the palliative care education, and attitudes toward end-of-life care. The authors concluded that students with more exposure to formal and informal palliative care education felt more prepared and were more positive about their end-of-life care education. Students with greater exposure to a hidden curriculum (medical interactions with implicit biases) that devalued end-of-life care rated their preparation as poor and had worse attitudes toward end-of-life care. (6) With the recognized need to augment the care provided to patients with severe life-limiting illness before death, the impetus has arisen for educational ventures that support this goal. The Institute of Medicine has recommended enhanced education in palliative care since 1997, though it is unclear to what degree this challenge has been fulfilled. (7) In 2017, Dickinson reviewed the history of course offerings from 1975 to 2015 in US medical schools. He concluded that 99% of US medical schools offered education on palliative care. This sounds impressive, but only about 12 to 15 hours of the entire medical school curriculum were devoted to palliative care topics; this duration remained steady in the last 15 years. (8)

PEDIATRIC PALLIATIVE CARE

Although adult patients have benefited from palliative care and hospice medicine for almost a century, pediatric patients have derived a similar benefit only in recent decades. (9) In 2012, Feudtner and colleagues conducted a survey of Children's Hospitals to ascertain whether they had a palliative care service among other things. Of the 162 hospitals that provided data, 69% stated that they had a pediatric palliative care program. (10) Compared with adults, pediatric patients are generally healthier. Thus, pediatric resident trainees may have limited opportunity throughout their training years to be exposed to such patients and develop comfort and skill in providing palliative care to those who may need it. Pediatric trainees who proceed to subspecialize in areas where the prevalence of death and disability is higher are relatively ill-prepared to provide care along the palliative care spectrum, especially near the end of life. (11) A study by Michelson et al assessed pediatric trainees including pediatric subspecialty fellows' perspectives on palliative care education. (12) The authors found that most respondents felt that they would benefit from more formal palliative care education. The 3 areas perceived to have deficits in education were discussing prognosis, delivering bad news, and pain control. (12)

PALLIATIVE CARE IN NEONATAL-PERINATAL MEDICINE

Neonatal-perinatal medicine is among those pediatric specialties in which patients have a higher risk of death than the rest of the pediatric population, and accounts for upwards of 30% of deaths in the pediatric age range. While death can happen spontaneously in an otherwise healthy neonate or infant in the home setting, the top 3 causes of mortality in children younger than 1 year are congenital anomalies, prematurity, and maternal pregnancy complications—conditions frequently seen in the NICU patient population. (13)

For the hospitalized at-risk neonate with an underlying life-threatening condition, death may occur as the result of a planned withdrawal of technology to permit a natural demise, or it may occur during an attempt at resuscitative measures despite a poor prognosis. Some newborns die during or slightly after the delivery process in the delivery room, while other chronically ill neonates may have a sudden unforeseen decompensation and die in a time frame that was somewhat unexpected. Occasionally, hospitalized neonates who were previously thought of as very low risk suffer unforeseen complications and unexpectedly die. No matter the cause, death at this very beginning phase of life is difficult to frame and process for families, staff, and trainees. (14) Thus, in this field where death is not uncommon, the need for palliative care services and first-line pediatric providers who are well-versed in the tenets of palliative care is urgent. (3)(15)

Guidelines for the initiation of palliative care in the NICU may include a comprehensive list of "trigger" conditions (not necessarily specific diagnoses) that help identify disease states that may portend a significantly shortened life span. (16)(17) Although patients may recover with significant morbidity, such as an extremely preterm infant at 22 or 23 weeks of gestation, others may recover to a significant extent such that the need for palliative care services decreases and ultimately ceases over time. Earlier inclusion of the comprehensive services that palliative care provides leads to enhanced care by strengthening the collaboration between the medical team and the neonate's family, which may facilitate advanced care planning and redirecting goals of care, should this be needed. (18)

EDUCATIONAL STRATEGY: AN EXAMPLE OF A MULTIMODAL FELLOW TRAINING MODEL

Emphasis on adult education strategies and the recognition of shortcomings within traditional lecture-driven training has given rise to several new learner-based curriculum models. The old adage of "see one, teach one, do one" no longer satisfies the rigorous requirement for high-quality credentialing and certification of clinical care skills. The advent of case-based curricula, flipped classroom methodology, and emphasis on simulation all support a paradigm shift toward adult-based learning approaches. (19)(20)(21) Simply dispensing and presenting knowledge in the traditional lecture setting does not ensure sustainable retention in learners and it is understood that "if you don't use it, you lose it." Hence learners must have the opportunity to practice skills that were taught, irrespective of the modality by which the material was introduced to them.

Difficult conversations, dispensing bad news, obtaining and reframing goals of care, and shared decision-making are "procedures" conducted daily in neonatal medicine, yet historically these are learned by trainees solely through modeled behavior. Training experiences are variable, contingent on the case mix within the unit at any given time, and inconsistent, because senior providers have a diverse repertoire of experiences and styles but may not adhere to best practice standards. However, these skills can be learned, practiced, and optimized in a way that is independent of how emotionally intuitive or expressive any individual trainee is. This is particularly important in an environment with diverse trainees of varying cultural and religious backgrounds and beliefs that may influence and bias feelings and communication in emotionally charged situations.

A multimodal curriculum was designed to teach neonatal palliative care to our 6 neonatal-perinatal medicine fellow trainees using adult-based learning theories as a foundation. Content selected reflects topics within the 8 domains of palliative care as outlined by the clinical practice guideline for quality palliative care (Table 1). (2) Protected time is provided to the fellows for 1.5 hours every month, and lectures are cofacilitated by the 2 directors of the Neonatal Palliative Care Team called Neo-Quality in Life Team (Neo-QuILT) who are attending neonatologists with advanced training in palliative care and difficult conversations.

A total of 12 sessions are held annually. Some sessions have a didactic component with queries posed for self-reflection and discussion. Other sessions are followed by simulated scenarios. Three sessions are purely simulated cases. Cases are modified versions of real patient scenarios from our own level 4 NICU and are chosen specifically to highlight topics emphasized in the lectures. Role play scenarios are presented to the fellows with progressive levels of difficulty; for example, first-year fellows are asked to give bad news, while third-year fellows are asked to have a conversation about redirecting care toward comfort care to a critically ill infant. The style of teaching is purposefully conversational and informal to give the fellows a safe space to vocalize their needs, concerns, and insecurities. Everyone is reminded about the rules for debriefing constructively at the start of each scenario and is asked to participate in providing meaningful feedback.

The American Academy of Hospice and Palliative Medicine recently published a model for education in palliative and end-of-life care in pediatrics for residents; this model describes identifying a "hook" or compelling anecdote to illustrate why a particular topic is important. (22) By providing context, the skill that is being taught is more apt to be integrated and recalled by the learner. We capitalize on this concept and modify scenarios in real time to reflect the needs of the fellows. For example, if there is a difficult case in the NICU that is being driven by a family's strong religious beliefs, we modify the timing of the session on religion and spirituality to have the greatest impact on the fellows. Similarly, if there are communication challenges or mixed messaging with a particularly distraught family in the NICU, we integrate the case into the didactic portion of the lecture related to communication to clarify techniques for improvement.

The monthly curriculum does not replace, but rather enhances the modeling method of education that remains ongoing. In an effort to augment learning opportunities, fellows are asked to attend all family meetings and, as senior fellows, to run them. Often, 1 of the Neo-QuILT providers is in attendance and holds a debriefing session with the trainee after the meeting to give real-time feedback, assess the content of the conversation, and identify opportunities for improvement. Fellows are also expected to attend antenatal consultations for birth planning for fetuses that have been identified as having a life-limiting anomaly. The same debriefing structure is applied to these sessions as well. Often concepts that were "easy" to simulate prove to be much more challenging to present to real patients. By applying the same structured feedback to real patient experiences as is applied in the simulations, the gap between an artificial learning environment and a real one is bridged.

To illustrate this point more clearly, a simulation was conducted with third-year fellows in neonatal-perinatal medicine to establish a plan for comfort care with a parent of a child with trisomy 13. This was the simulation conducted during the "Establishing Goals of Care" lecture within the palliative care curriculum. Although the fellow participating stumbled a bit during this simulation, she met the objectives of the case and held a constructive fictional family meeting. Three months later, a parallel situation presented itself in the NICU. The same third-year fellow led the family meeting in which the end of life and goals of care became the focus of conversation. In this real-life scenario, she fumbled with diction and sped through her recommendations without pausing to allow the family time to process. She was also challenged by unexpected emotional queries by the family such as, "Why didn't she care about their baby?" She was guided and supported appropriately by the attending neonatologist in the meeting. After the meeting, the Neo-QuiLT provider, who was in attendance, was able to debrief with the fellow using the same format that is used during simulation. By discussing the case and meeting in a familiar, nonthreatening, and constructive way, she was able to identify her shortcomings and areas for improvement.

Over the 3 years of the neonatal-perinatal medicine fellowship, depending on the fellows' call schedule, they are exposed to each of the lectures 3 times (once per year). The hope is that escalating experience and personal growth over the 3 years of fellowship allows the same participant to have a differential learning experience even with the same material. For example, during the communication lecture, first-year fellows may grasp the importance of good communication especially at times of high stress. During simulation, they may also observe and experience a few examples of phrases or sentiments that are useful in enhancing communication during a difficult conversation. As second-year fellows exposed to the same lecture, and hopefully having observed and participated in a few real-life experiences of difficult conversations, they may now have a better idea of what expressions and actions resonate with them, as well as understand and manage their emotions during a difficult conversation. Third-year fellows are expected to have more insight into their own emotions and those of the family, be able to show empathy, and be able to fluidly adjust during the conversation. These senior trainees should be comfortable using a range of expressions, both spoken and physical, to express their thoughts meaningfully, verbally acknowledge what the family is saying and feeling, and be able to construct a care plan that represents collaboration between the family and medical team.

Benefits and Pitfalls

There is extensive literature highlighting the extreme anxiety and lack of confidence trainees feel in navigating conflicts between staff and/or patients as they relate to end-of-life care and chronic illness. (22)(23)(24) Giving them a forum to practice terminology and phrasing in an inconsequential way bolsters their skills while enabling them to modulate and shape their own personal style of communication. It serves as an outlet to explore their explicit and implicit biases' and opinions and decipher what role those opinions should have, if any, in shared decision making. The informal nature of the sessions allows senior fellows to share experiences that went well or poorly for them, or which they felt particularly challenged them, and skills they found helpful. In the unnamed and unofficial role of group cofacilitator, they are solidifying their own practice by articulating behaviors that may have started as unconscious and innate yet have evolved into skills that are practiced and learned via the palliative care curriculum.

An unanticipated secondary gain of this curriculum is to enhance wellness within the neonatal fellowship. The topics selected for each lecture naturally lend themselves to discussions about the more challenging and morally distressing NICU cases. The conversation seamlessly transitions and incorporates thoughtful discussions about cases that are actively troubling to the fellows. They use this time to dissect what emotions they are experiencing, how to process them, how to incorporate strategies that will help them to reconcile a family's decision if it does not resonate with their own personal beliefs, and sometimes just grieve a loss together as a group. These sessions often become tearful and are emotionally fraught. Expressions of guilt, fatigue, and frustration are common. Rarely, they may become contentious if people's strong personal beliefs about death, dying, and spirituality do not align with those of a family or their colleagues. The facilitators are charged with de-escalating and reframing the discussion in a way to unify the group and mitigate moral suffering.

Although this diversion from the curriculum is often fellow initiated, it is sometimes driven by the Neo-QuiLT facilitators to address a recent dilemma or clinical conflict in a productive way. Division leadership has recognized the positive impact of the sessions and intermittently use the conferences as an opportunity to highlight the importance of interprofessional collaboration. Specifically, we focus on communication and meaningful messaging. Such sessions are successful, but largely because they are conducted in a nonjudgmental and nonconfrontational way, and they fall outside the intended parameters and goals of the palliative care curriculum. We refer to these extraneous conversations, agenda topics, and debriefs as a hidden curriculum that has emerged unexpectedly and underscores the need for a companion trainee wellness curriculum. Resiliency and mitigating burnout are of paramount importance and given priority when it is deemed necessary. However, tangential conversations of this nature are time consuming and occasionally derail the curriculum. Consequentially, stated objectives are not met.

There are other limitations to implementing a successful formal palliative care curriculum. Logistical issues such as timing sessions around facilitator service schedules, facilitator and fellow vacations, and call schedules preclude full attendance at all times. There are only 2 Neo-QuiLT providers and it is impossible for them to attend all family meetings to do real-time debriefs. Some fellows may share a particularly close personal relationship with one another, while others have tumultuous relationships. Furthermore, personality types vary and some are more symbiotic than others. In an informal setting, as outlined within this curriculum, underlying tension and personality dissonance can be disruptive or even obstructive to learning. The fellows will often speak about their personal perceptions of their capabilities; at times, these do not align with feedback that the Neo-QuiLT facilitators have received from colleagues and ancillary staff. It is important to address any lack of insight and mitigate conflicts; however, without formal real-time 360-degree feedback, it must be handled in a delicate way.

Finally, the metrics of successful implementation of a palliative care curriculum remain poorly defined. Although the fellows have expressed that they feel positively about the sessions, how can we translate this sentiment to quantitative improvement in communication skills, symptom management for the dying infant, and support for a family? Likewise, is this improvement attributable to the curriculum or would this comfort level be the same as the trainee progresses through any fellowship, regardless of structured educational sessions?

Metrics of Success

With any formalized curriculum, it is important to assess metrics of success to be able to make changes for both the learners and the instructors. Adults learn in a variety of ways. A well-rounded palliative curriculum will initially draw from various types of educational modules and reflection on personal experiences. Based on the chosen evaluation measures, the curriculum will be changed to maximize its effects on the learners. Suggested means of assessing the effectiveness of the education include the educator's formal evaluation of the bedside performance of the trainee with actual patients and families, self-administered surveys to trainees, surveys to other members of the medical team and families (360-degree evaluations), and learner performance on simulated cases with real-time 2-way (learner and educator) debrief and feedback. The pros and cons of different evaluation methods in the palliative care curriculum are summarized in Table 2. Another indirect way of assessing success of the palliative care education includes feedback from fellows during the annual fellowship program review. Other assessments of fellow performance as it pertains to palliative care are occasionally indirectly brought to light by presentations such as case reviews, morbidity and mortality discussions, and quality improvement meetings.

Regardless of whether some or all of the methods listed in Table 2 are used for evaluating the learner's response to palliative care education, having a dynamic and open feedback process is essential. Learners may themselves act unknowingly as teachers in group debriefs and discussions. Educators may find themselves learning new viewpoints as well.

SUMMARY

Palliative care is an important aspect in the care of critically ill neonates, especially those likely to die or live with significant morbidity. There are challenges in identifying neonates who are appropriate candidates for receiving palliative care services before imminent death. By delaying palliative services, opportunities may be lost to build relationships, perform adequate redirecting of goals, and appropriately integrate essential palliative care principles into the care of the neonate. Many physicians exhibit discomfort or unfamiliarity with the integration of palliative care measures in the care of infants, leaving neonatal-perinatal trainees underexposed to the benefits of such care. Families benefit significantly from enhanced communication, symptom management, and overall multidisciplinary care planning when palliative care services are offered to severely ill children in the NICU. Hence, a structured curriculum for neonatal-perinatal medicine fellows to enhance and optimize this skill set is warranted.

TABLE 2. **Methods of Evaluation of a Palliative Care Curriculum for Neonatal Fellows**

METHOD OF EVALUATION OF PALLIATIVE CARE CURRICULUM	PRO(S)	CON(S)
Formal evaluation of bedside interaction with family	Usually a predesigned tool with delineated goals	Learner may focus on the delineated goals as items to be performed but may miss the nuanced fluidity of the interaction
Fellow self-evaluation	Educator may gain important insight into fellows' perceptions of their knowledge, comfort, and skill in delivering palliative care, and tailor future educational activity accordingly to suit learners' specific needs	May not reflect reality because the experience is subject to trainees' personalities and experience level
Performance on simulated cases (with specific goals delineated)	• Replicates a real-life scenario in a safe space • Can be repeated with various parameters changed to maximize learning • Use of timeouts/pauses and time-ins may facilitate learners' ability to think through their next steps and re-enter the simulated encounter without penalty	Some learners have incredible anxiety in role-playing/simulations which may detract from executing skills they may intuitively possess and have used in a real scenario but have difficulty doing so in a contrived scenario
360-degree evaluations by other staff and families	Increases self-awareness and promotes ability to think through how others are affected by learners' actions even when unintended	The focus on the patient and family may be diminished as learners shift attention to additional participants

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the components of bereavement counseling prior to, during, and after the death of a newborn infant, including palliative care.

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Iron Nutrition, Erythrocytes, and Erythropoietin in the NICU: Erythropoietic and Neuroprotective Effects

Pamela J. Kling, MD*

**Department of Pediatrics, University of Wisconsin, Madison, WI*

Education Gaps

1. Clinicians should recognize that congenital iron deficiency (ID), defined by inadequate placental-fetal iron transfer, can be detrimental to neurocognitive development.
2. Clinicians should recognize that delayed umbilical cord clamping at birth can improve neonatal iron status and favorably impact neurocognitive development.
3. Clinicians should know that erythropoietin/erythrocyte-stimulating agents (Epo/ESA) can favorably impact neurocognitive development.

Abstract

Prematurity, maternal diabetes, maternal smoking, being medically underserved, and small size for gestational age are common characteristics of neonates in the NICU and can predispose them to develop congenital iron deficiency. Iron is critical for organ development. In the fetus and newborn, iron is prioritized for red blood cell production, sometimes at the expense of other tissues, including the brain. It is critical to optimize iron levels in newborns to support erythropoiesis, growth, and brain development. Available studies support improved neurodevelopmental outcomes with either iron supplementation or delayed umbilical cord clamping at birth. Erythropoietic doses of erythropoietin/erythrocyte-stimulating agents may also improve neurocognitive outcomes. However, the literature on the effect of liberal red blood cell transfusions on long-term neurodevelopment is mixed. Understanding age-specific normal values and monitoring of iron indices can help individualize and optimize the iron status of patients in the NICU.

Objectives After reading this article, readers should be able to:

1. Describe the causes of congenital iron deficiency and explain strategies to optimize iron status in at-risk infants.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
DCC	delayed cord clamping
ECC	early cord clamping
Epo	erythropoietin
ESA	erythrocyte-stimulating agent
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
ID	iron deficiency
LGA	large for gestational age
NNT	number needed to treat
RBC	red blood cell
SGA	small for gestational age
USPSTF	US Preventive Services Task Force

2. Develop an approach to include iron status as a neuroprotective strategy in the NICU.

ROLE OF IRON IN DEVELOPMENT

Fetal Iron Acquisition and Iron in Development

Iron is required for the development of all organs, including the brain. Normally, 75% of neonatal body iron is transferred in the third trimester, and thus, premature neonates are at increased risk for congenital iron deficiency (ID). (1) Up to 80% of the total body iron amount is found in red blood cells (RBCs) at birth. In acute or chronic fetal hypoxia, maternal diabetes, and placental insufficiency, iron utilization in the fetus is driven by erythropoietin (Epo) production and is prioritized for RBCs at the expense of the brain and other organs. Most healthy term infants born after uncomplicated pregnancies have sufficient iron stores to last until 4 to 6 months of age, largely because of their higher blood volume relative to body weight. For neonates with congenital ID, human milk is a negligible iron source because the iron content is relatively low (0.35 mg/L). (2)

In practice, congenital ID has become relatively common and can be seen if there is a maternal history of placental insufficiency, untreated ID, diabetes, obesity, smoking, alcohol ingestion, and psychosocial stress. Congenital ID is more likely to occur in certain medically underserved, lower socioeconomic status, and ethnic populations, especially Mexican Americans. Congenital ID can also occur in multifetal gestation pregnancies, preterm infants, and small- and/or large-for-gestational age (SGA or LGA, respectively) infants; boys have a greater predisposition toward congenital ID. (2)(3)(4)(5)(6)(7) Premature infants are particularly at risk, with up to 17% of premature infants exhibiting congenital ID. (8) The Fig shows that many fetal exposures and conditions can disrupt normal fetal iron endowment, predisposing neonates to congenital ID, and outweigh the limited number of modifiable factors that can balance fetal-neonatal iron status.

Identification of those neonates with congenital ID is important. Dozens of studies have shown that infants who are born with congenital ID (9)(10)(11) or develop ID during early infancy are at risk for adverse long-term neurocognitive, sensory, and/or behavioral consequences. (12) Mechanistic studies support the idea that ID has an adverse impact on cell division, neuronal growth, dendrite branching, myelination, neurotransmitter production in sensory organs, and hippocampal memory centers. (12) Although sleep disturbances, breath-holding spells, febrile seizures, irritability, restless legs syndrome, apathy, and depressive symptoms are known neurobehavioral signs of older children with ID, the adverse neurobehavioral impact is most pronounced and persistent in cases of ID during the first 1,000 days of active brain development.

Postnatal Iron Status, Anemia of Prematurity, and Phlebotomy

Premature infants lack sufficient iron and this iron deficit is more severe in lower gestational age infants. Premature infants also experience an exaggerated anemia of prematurity compared with the physiologic nadir seen in term infants. This anemia of prematurity occurs because preterm infants have low levels of Epo, a shortened RBC survival, and relatively rapid postnatal growth with greater hemoglobin synthesis to support blood volume expansion. A small circulating blood volume relative to iatrogenic blood loss is the most dominant factor, leading to coining of the term "anemia of phlebotomy." For example, typically, a 1,000-g birthweight infant is born with a hemoglobin concentration of 15 g/dL (150 g/L), blood volume of 90 mL, RBC mass of 40 mL, and total body iron of 77 mg. In the absence of RBC transfusions, an estimated 28 mL of phlebotomy losses in the first 2 months removes 15 mg of iron, which corresponds to 18% of the fetal iron endowment. (1) These losses require more than 1 mg of iron daily (double that of term infants) to support growth during the first year. Because some centers report relatively lower phlebotomy losses in even very-low-birthweight infants, developing a strategy to minimize NICU phlebotomy losses has merit.

Oral iron is also effective at improving iron stores in infants with ID. In a systematic review of low-birthweight infants, between 0.6 and 6 mg/kg per day of oral iron started between the first and fifth week of age prevented ID anemia at 6 to 12 months (number needed to treat [NNT] = 5). (13) RBC transfusions are an excellent iron source. Among very-low-birthweight infants, the need for RBC transfusions is greatest in those at the lower end of the range, with a lower initial hemoglobin, immediate cord clamping, greater phlebotomy losses, and greater illness acuity, (14)(15) though RBC transfusion practices vary widely. (16)

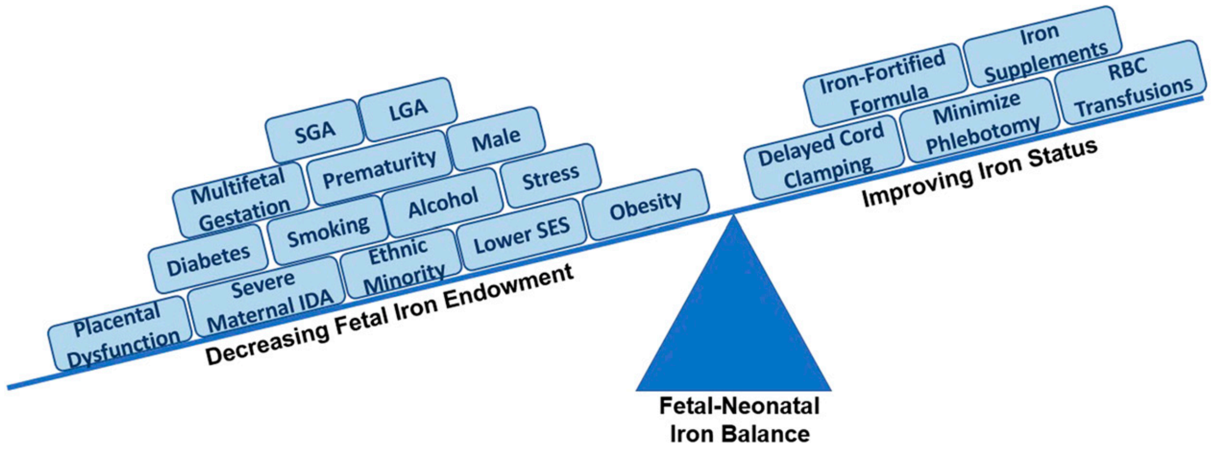

Figure. Fetal-neonatal iron balance. The forces that decrease fetal iron endowment, predisposing to congenital iron deficiency, can outweigh the modifiable factors that improve iron status in at-risk infants.

Neurocognitive Outcomes with Phlebotomy and RBC Transfusions, in Relation to Iron Status

Phlebotomy-induced anemia (and iron loss) in animal models has a negative impact on brain development. (17) Both ID and a relative anemic hypoxemia are known to regulate important cell functions active in developing brain hippocampal neurons linked to learning and memory. (12)(18) Two large randomized studies of restrictive versus liberal RBC transfusion triggers in premature infants examined neurocognitive outcomes. (19)(20) Hemoglobin transfusion trigger number rose with greater acuity, but hemoglobin triggers were generally 25% higher in the liberal than the restrictive transfusion groups. These well-designed studies found conflicting short-term (19)(20)(21) and long-term outcomes. (22)(23)(24) In 1 study, the restrictive RBC transfusion group had more intraparenchymal or periventricular hemorrhages, (19) while a second study found that neurologic brain injury at hospital discharge did not differ between the restrictive and liberal transfusion groups. (20) In follow-up, the first study (19) unexpectedly found less white matter volumes in toddlers in the liberal transfusion group (23) that adversely affected function in school-age girls. (24) The second study (25) found that death, cerebral palsy, cognitive delay, or hearing loss did not differ by transfusion strategy, but found higher Bayley Scales of Infant Development Mental Development Index in toddlers with liberal transfusions. (22) Thus, the impact of RBC transfusions in long-term neurocognitive developmental function is not clear.

The effect of oral iron supplementation on neurocognitive development in infants has also been studied. A study of preterm and late preterm infants given iron supplements early (at 2 weeks of age) versus late (at 6 weeks of age) found neither harm nor benefit of early iron, (26) but a second study found that iron given early (at 6 weeks of age) as opposed to late (at 6 months of age) led to improved behavior, (27) with a third study showing better neurologic findings if given at 6 weeks versus 6 months. (28) A systematic review found that the NNT was 5 if iron was given early versus late. (13) Although SGA infants (6) and LGA infants of diabetic mothers (11)(29) are at increased risk for neurocognitive deficits due to congenital ID, any benefit from early iron supplementation is yet to be established. However, randomizing breastfed term infants to early iron supplements (at 6 weeks vs 6 months) and testing in late infancy showed better visual acuity in 1 study (30) and better Bailey psychomotor indices in a meta-analysis (NNT=14). (31) In a long-term study, socioemotional advantages were found in iron-supplemented infants, which persisted to 10 years of age. (32)

ERYTHROCYTE ENDOWMENT AND IRON

Delayed Umbilical Cord Clamping and Iron Status

In addition to other benefits, the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (33) recommend delayed cord clamping (DCC) at nearly all vaginal births to improve the RBC iron endowment of infants. In premature infants of less than 37 weeks' gestation, DCC leads to a 10% to 15% increase in the initial RBC volume and decreases the need for RBC transfusions compared with early cord clamping (ECC). (34)(35)(36) In a Cochrane systematic review, DCC in infants born before 37 weeks' gestation was associated with a higher hemoglobin concentration, fewer RBC transfusions, and decreased intracranial hemorrhages compared to infants with ECC. (36) A recent review of DCC in extremely preterm infants confirmed fewer RBC transfusions and intracranial hemorrhages, with higher overall survival. (37) DCC translates into improved short- and long-term iron status in term and preterm infants. (35) Late preterm and term SGA infants with DCC experienced better iron status at 3 to 6 months of age (NNT=16). (38) DCC was also effective during cesarean births, showing better iron status in infants at 4 months of age compared with infants who had ECC. (39) Cord milking was also effective, with ferritin status after milking comparable to DCC at 6 weeks, 6 months, or 12 months of age. (40)

Neurocognitive Outcomes with DCC

Although it is not known whether iron plays a role, neurocognitive function was better in term infants after DCC (NNT=10). (41) In very preterm infants, DCC decreased death or adverse neurodevelopmental outcome at age 2 years (NNT=8). (42) Cord milking in premature infants was comparable to DCC, with similar cognitive composite scores seen at 2 years of age. (43) A mechanistic study of DCC found that better iron status at age 4 months in term infants was directly related to myelin content in the internal capsule and other regions associated with motor, visual, and sensory processing. (44) In addition to better myelination, the decreased risk for intracranial hemorrhage or retinopathy in premature infants could also contribute to improved neurocognitive outcomes in DCC. (45)

ERYTHROPOIETIN AND IRON

Epo/Erythrocyte-Stimulating Agents for Treating Anemia of Prematurity and Iron Status

Dozens of published studies report that treatment with Epo or erythrocyte-stimulating agents (ESA) prevents the need for RBC transfusions in preterm infants. Although heterogeneous, the studies found that the need for RBC transfusions often cannot be eliminated in the smallest infants, even when Epo/ESA therapy is begun early (<8 postnatal days). (46)(47)(48) Thus, although Epo/ESA therapy is used in NICUs, it has not been uniformly adopted. Iron supplements and iron status monitoring are necessary with Epo/ESA therapy. Although parenteral iron dosage of 1 mg/kg daily or 6 mg/kg weekly was reported in Epo/ESA studies, most studies used oral iron supplements of 2 to 6 mg/kg daily. Although studies are heterogeneous, systematic reviews and meta-analyses conclude that whether starting early (<8 postnatal days) or late (≥8 postnatal days), administration of Epo/ESA decreased the number of RBC transfusions (NNT=6–7). (47)(48)

Neurocognitive Outcomes with Epo/ESA Therapy

Exogenous Epo/ESA exerts neuroprotective effects in animals. Human studies are ongoing to assess whether high-dose Epo (>1,000 U/kg per day) in the first days after birth is neuroprotective for infants with prematurity and/or hypoxic-ischemic encephalopathy. Several studies have examined the effect of lower erythropoietic dosing (<1,000 U/kg per week) to prevent RBC transfusions. Early dosing of low-dose Epo/ESA before age 8 days to prevent RBC transfusions may lower the incidence of intracranial hemorrhage (NNT=25). (47) In a Cochrane systematic review, early erythropoietic dosing of low-dose Epo/ESA before age 8 days in preterm and/or low-birthweight infants also improved neurodevelopmental outcome (NNT=13). (47) After early low-dose Epo/ESA therapy, improved neurocognitive outcome in toddlers or preschoolers (49)(50)(51) have been shown to be affected by socioeconomic status (51) or higher peak Epo levels. (49)

SCREENING FOR AND TREATING IRON STATUS

Screening Iron Status in NICU

Because iron sufficiency during early life may improve neurocognitive outcomes, (12) defining iron status precisely in at-risk infants and treating those with ID appropriately should be considered a neuroprotective strategy. In older children, ID progresses in stages, but the stages are camouflaged by the postnatal hemoglobin nadir. Plasma ferritin levels fall as postnatal age rises. However, age-specific values are known and can guide interpretation (Table). The lower cutoff for normal plasma ferritin in prematurity is much higher than the textbook normal value of 12 μg/L (26.4 pmol/L). Close monitoring of iron status is needed for Epo/ESA–treated infants. During Epo/ESA therapy, plasma ferritin values of 65 to 100 μg/L (146–225 pmol/L) are considered to be cutoff values in premature infants. The lower limit is supported by the physiologic observation that plasma ferritin of less than 70 μg/L (<157 pmol/L) at 6 weeks' postnatal age predicted the development of ID anemia at 6 months in nonsupplemented breastfed preterm infants. (8) RBC indices complement plasma ferritin and are sensitive measures of ID erythropoiesis; these include a low mean corpuscular volume, an elevated red cell distribution width, and low reticulocyte hemoglobin content (Table). (52)

Very premature infants may benefit from an individualized approach that includes screening, with a complete blood cell count and plasma ferritin level at 1 to 2 months of age, hospital discharge, 6 months of age, and 12 months of age, especially in infants who are receiving mostly human

TABLE. **Age-Specific Iron Values in Preterm and Term Infants**

	PRETERM (SI UNITS)[a]	NORMAL RANGE (SI UNITS)	TERM (SI UNITS)	NORMAL RANGE (SI UNITS)
Cord blood				
Hemoglobin	16.8 g/dL (168 g/L)	13.0–20.6 g/dL (130–206 g/L)	17.9 g/dL (179 g/L)	14.0–22.0 g/dL (140–220 g/L)
Reticulocyte hemoglobin	35.6 pg	31–38 pg	35.6 pg	31–38 pg
Plasma ferritin	115 μg/mL (258 pmol/L)	35–267 μg/L (70–600 pmol/L)	134 μg/L (301 pmol/L)	40–309 μg/L (90–694 pmol/L)
Zinc protoporphyrin/heme	105 mmol/mol	48–184 mmol/mol	72 mmol/mol	35–178 mmol/mol
Age 1-2 mo				
Hemoglobin	10.7 g/dL (107 g/L)	8.9–13.5 g/dL (89–135 g/L)	13.9 g/dL (130 g/L)	9.5–17.9 g/dL (95–170 g/L)
Reticulocyte hemoglobin	27.8 pg	26.1–27.1 pg	26.8 pg	23.2–30.4 pg
Plasma ferritin	129 μg/L (290 pmol/L)	50–232 μg/L (112–521 pmol/L)	157 μg/L (353 pmol/L)	67–300 μg/L (150–674 pmol/L)
Zinc protoporphyrin/heme	187 mmol/mol	52–292 mmol/mol	88 mmol/mol	45–121 mmol/mol

[a] *Data on preterm infants are from those who are not receiving therapy with erythropoietin/erythrocyte-stimulating agent or red blood cell transfusions.*

milk. Late preterm infants or ill term infants may benefit from screening, with a complete blood cell count and plasma ferritin level at 6 and 12 months of age. Avoiding screening during an acute illness or recent immunizations will prevent artifactual elevations of ferritin, which is an acute phase reactant. In non-NICU healthy infants, despite the US Preventive Services Task Force (USPSTF) reporting insufficient evidence for universal screening of all infants for ID, (53) the AAP recommends universal screening 9 to 12 months after birth. (2)

Iron Supplementation in Early Life

The AAP and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommend that all infants born before 37 weeks' gestation who are breastfed should receive at least 2 to 3 mg/kg per day of supplemental elemental iron through 12 months of age. (2)(54)(55) Both organizations agree that human milk is an inadequate iron source for low-birthweight late preterm infants, a population unlikely to receive a transfusion, reinforcing the need for early supplementation. (8) The AAP and ESPGHAN recommend supplementation with iron up to age 6 months at a dose of 2 to 3 mg/kg per day for term infants with a birthweight less than 2,000 kg and a dose of 1 to 2 mg/kg per day for term infants with a birthweight between 2,000 and 2,500 g, (55) especially if exclusively breastfeeding. In otherwise healthy exclusively breastfed term infants, the AAP recommends supplements of 1 mg/kg per day elemental iron starting at age 4 months and continuing until the infant is receiving sufficient iron from iron-containing complementary foods (2) (Note: the USPSTF does not make this recommendation). Both the USPSTF and AAP recommend iron supplementation of LGA infants who remain above the 95th percentile for weight during infancy due to iron needs for growth. (2)(53) With typical intake, formulas in the United States are fortified with approximately 4 to 5.5 mg/kg per day of iron; thus, late preterm and at-risk term NICU graduates typically receive sufficient iron if they are exclusively formula-feeding.

If an infant is receiving Epo/ESA therapy, iron supplementation at a dose of 2 to 6 mg/kg daily is recommended. However, ID-erythropoiesis can still be seen, making it important to monitor iron status in infants receiving Epo/ESA therapy. Parenteral iron can be given with early Epo/ESA treatment, (56)(57) but because of theoretical iron toxicity risks, caution should be used when combining parenteral iron and RBC transfusions. Because of the iron load received from multiple RBC transfusions, some NICUs hold iron supplements for 1 to 2 weeks after RBC transfusions.

CONCLUSION

Understanding iron balance should be considered as part of a neuroprotective strategy for both NICU patients and those infants who are discharged. DCC, minimizing phlebotomy losses, providing transfusions when necessary, early iron supplementation, and potentially treating with erythropoietic doses of Epo/ESA for anemia of prematurity may all confer neurocognitive benefits for ill neonates in the NICU.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical indications for use of blood products in neonates, as well as the manifestations and prevention of potential complications of transfusion.
- Know normal erythropoiesis in the fetus and neonate.
- Know the factors regulating erythropoiesis in the fetus and neonate including erythropoietin.
- Know the causes of and diagnostic approach to an infant who is anemic at birth.

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1. A neonate born at 25 weeks' gestational age is now 2 weeks old and has transitioned to full enteral feedings. Oral iron supplementation is being initiated. In the typical process of fetal development, approximately what percentage of neonatal body iron would have been transferred in the third trimester?
    - A. 25%.
    - B. 33%.
    - C. 50%.
    - D. 75%.
    - E. 90%.
2. A 26-week gestational age male neonate, with birthweight of 1,000 g, is 1 week old and receiving partial parenteral and partial enteral feedings. He is receiving continuous positive airway pressure. Blood specimens are obtained for routine laboratory tests according to the unit's protocol. Which of the following statements regarding anemia in preterm neonates is correct?
    - A. Phlebotomy is a large contributor to anemia of prematurity, because of the small circulating blood volume relative to iatrogenic blood loss in preterm neonates.
    - B. A regular controlled schedule of phlebotomy leads paradoxically to decreased anemia over time because of a more robust stimulation of erythropoietin production.
    - C. Compared with the physiologic nadir of anemia seen in term infants, preterm neonates have relatively less progression of anemia during the first month after birth.
    - D. The typical blood volume of a 1,000-g birthweight neonate is 210 mL.
    - E. It is neither safe nor efficacious to provide enteral iron supplementation to infants until they reach term-corrected gestational age.
3. A neonate born at 33 weeks' gestational age received delayed cord clamping for 60 seconds. The neonate breathes spontaneously at birth and does not require respiratory support. Which of the following is correct regarding the impact of delayed versus immediate or early cord clamping during vaginal birth?
    - A. In preterm neonates born before 37 weeks' gestational age, delayed cord clamping leads to a 10% to 15% increase in the initial red blood cell volume.
    - B. For neonates of less than 34 weeks' gestational age, delayed cord clamping is associated with a higher incidence of any intraventricular hemorrhage, but no difference in severe (grade 3 or 4) intraventricular hemorrhage.
    - C. Delayed cord clamping increases hematocrit values in the first 2 weeks after delivery but is not associated with any change in iron status.
    - D. There have not been any studies indicating that neurocognitive function is improved with delayed cord clamping, in either preterm or term infants.
    - E. Large population-based studies have shown that delayed cord clamping is associated with higher achievement in college, and quicker progression to management level positions in professional careers.
4. A male 27-week gestational age infant is 5 weeks old and has been treated with erythropoietin during the hospital course thus far. Which of the following would be a finding consistent with iron-deficiency anemia?
    - A. High plasma ferritin level.
    - B. High mean corpuscular volume.
    - C. Low red cell distribution width.
    - D. Low reticulocyte hemoglobin content.
    - E. Elevated β-hydroxybutyrate level in red blood cells.

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5. A female infant born at 31 weeks' gestational age is now 5 weeks old and getting ready to transition to the home. The neonate is primarily receiving her mother's breast milk. The team has considered growth to be adequate over the hospital course, including the most recent week. Which of the following considerations for iron supplementation is correct for this neonate?
   - A. The optimal source of iron is through infant formula, and the feedings over the next several months should be half breast milk and half infant formula fortified with iron.
   - B. While continuing to breastfeed, the infant should receive at least 2 to 3 mL/kg per day of elemental iron through 12 months of age.
   - C. Supplemental iron is only likely to be beneficial for this infant if there is a requirement for blood transfusion during the hospitalization.
   - D. Human milk is considered an adequate iron source, and iron supplementation should only be considered after testing the breast milk to check for iron status.
   - E. The optimal treatment strategy for iron-deficient preterm infants is to give the mother supraphysiologic oral iron supplementation, which can be transferred via breastmilk in a form that is easily absorbable by the infant's digestive tract.

Iron Nutrition, Erythrocytes, and Erythropoietin in the NICU: Erythropoietic and Neuroprotective Effects

Pamela J. Kling

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Iron Nutrition, Erythrocytes, and Erythropoietin in the NICU: Erythropoietic and Neuroprotective Effects

Pamela J. Kling

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Hyperglycemia in Extremely Preterm Infants

Sara Ramel, MD,* Raghavendra Rao, MD*†

*Department of Pediatrics, Division of Neonatology, University of Minnesota, Minneapolis, MN

†Center for Neurobehavioral Development, University of Minnesota, Minneapolis, MN

Education Gaps

1. Despite its common occurrence, the significance of hyperglycemia for short- and long-term outcomes in extremely preterm infants is not well understood.
2. There are wide variations in the criteria used for managing hyperglycemia and treatment methods.

Abstract

Hyperglycemia after birth is common in extremely preterm infants (<28 weeks of gestation). Lower gestational age, lower birthweight, presence of severe illness, and higher parenteral glucose intake increase the risk for hyperglycemia, while provision of higher amounts of amino acids and lipids in parenteral nutrition and early initiation and faster achievement of full enteral feeding decrease the risk. Hyperglycemia is associated with increased mortality and morbidity in the neonatal period. Limited data show an association with long-term adverse effects on growth, neurodevelopment, and cardiovascular and metabolic health. Lowering the glucose infusion rate and administration of insulin are the 2 treatment options. Lowering the glucose infusion could lead to calorie deficits and long-term adverse effects on growth and neurodevelopment. Conversely, insulin use increases the risk for hypoglycemia and requires close blood glucose monitoring and frequent adjustments to glucose infusion and insulin dosage. Randomized trials of varying strategies of nutrient provision and/or insulin therapy and long-term follow-up are needed to improve clinical care and overall health of extremely preterm infants with hyperglycemia.

Objectives After completing this article, readers should be able to:

1. Describe the epidemiology, pathophysiology, and short- and long-term complications of hyperglycemia in extremely preterm infants.
2. Implement practice modifications to lessen the risk and impact of hyperglycemia.
3. Rationalize the choice of lowering the glucose infusion rate versus administering insulin as a treatment strategy.

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ABBREVIATIONS

CGM	continuous glucose monitoring
IVH	intraventricular hemorrhage
OR	odds ratio
ROP	retinopathy of prematurity
VLBW	very low birthweight

INTRODUCTION

Hyperglycemia is common in extremely preterm (<28 weeks of gestation) or very-low-birthweight (VLBW; <1,500 g) infants. Glucose infusion is essential for providing nutrition and preventing hypoglycemia in these infants. Unfortunately, an inability to handle the infused glucose predisposes this group to develop hyperglycemia. Hyperglycemia is associated with adverse short- and long-term outcomes in these infants. The mechanisms underlying these associations are not well understood. Coupled with a nonuniform definition and wide variations in the criteria used for management decisions as well as in the choice of treatment, these factors have led to confusion about the significance of hyperglycemia in extremely preterm infants.

EPIDEMIOLOGY

Definition

Hyperglycemia is typically defined as a blood glucose concentration greater than 125 mg/dL (>7 mmol/L) or a plasma glucose concentration greater than 150 mg/dL (>8.3 mmol/L). The greater than 150 mg/dL value has some physiologic relevance because it corresponds with renal glucose threshold in VLBW infants. (1) However, there is a wide variation in threshold glucose concentrations used for defining hyperglycemia. (2) Some studies further categorize hyperglycemia as mild, moderate, and severe, yet there is no uniformity in the criteria used for such categorization. Some studies have used absolute blood glucose concentrations, whereas others have used number of episodes or duration of hyperglycemia for defining severity. (3)(4)(5)(6)(7)(8)(9)

Incidence and Duration

The incidence of hyperglycemia in VLBW infants has varied from 15% to more than 80% in published studies, depending on the definition. (6)(10)(11)(12)(13) The incidence was 43% and 80% in the 2 studies that have used continuous glucose monitoring (CGM) in the first week after birth. (4)(6) Hyperglycemia is typically diagnosed within 48 hours after birth and peak glucose concentrations are seen toward the end of the first week. (4)(10) CGM in 188 VLBW infants during the first week after birth showed that 32% had a blood glucose concentration greater than 144 mg/dL (>8 mmol/L) for more than 10% of time (defined as mild hyperglycemia), 32% had a blood glucose concentration greater than 180 mg/dL (>10 mmol/L) for more than 10% of time (moderate hyperglycemia), 9% had a blood glucose concentration greater than 270 mg/dL (>15 mmol/L) for more than 10% of time (severe hyperglycemia) and 9% had 1 or more blood glucose concentrations greater than 360 mg/dL (>20 mmol/L; uncontrolled hyperglycemia). (4) There was no significant day-to-day variation in the prevalence of each of these glucose thresholds. Hyperglycemia in VLBW infants typically resolves by 2 weeks, (4)(10) likely because of improved insulin secretion over time. (14) However, the duration also could be reflective of the length of monitoring in those studies. A recent study of extremely preterm infants, where glucose monitoring continued until 28 days after birth, showed that approximately 20% had a blood glucose concentration greater than 180 mg/dL (>10 mmol/L) in the fourth week. (12) Other studies using CGM demonstrated the presence of hyperglycemia (blood glucose concentrations ≥140 mg/dL [≥7.8 mmol/L]) lasting over 30 minutes in 37% to 83% of clinically stable 4- to 8-week-old VLBW infants receiving bolus enteral feeding. (15)(16)(17) These late hyperglycemia episodes typically occurred in the postprandial period, were not related to the frequency of feeding, and were often followed by hypoglycemia. (15)(16)(17)

Determinants

The risk and severity of hyperglycemia vary inversely with gestational age and birthweight. (4)(10)(11) Sex-specific differences in insulin secretion (higher secretion in girls) as well as in the incidence of hyperglycemia (higher incidence in boys) have been reported in some studies, but not in others. (10)(18) Additional factors contributing to hyperglycemia include the following: a longer duration of parenteral nutrition; higher parenteral carbohydrate intake; conditions such as pain, sepsis, and higher illness scores; and medications such as steroids, theophylline, and vasoactive agents. (4)(6)(11)(12)(19)(20) Glucose infusion rates higher than 6 mg/kg per minute may also increase the risk. (4)(10)(20) However, not all studies have found this effect, and hyperglycemia may develop at lower glucose infusion rates.

PATHOGENESIS

The pathogenesis of hyperglycemia in extremely preterm infants is multifactorial. Principal factors are relative hypoinsulinism caused by a combination of defective processing of proinsulin to insulin in pancreatic β cells, less abundant peripheral insulin-sensitive tissues, and incomplete suppression of glucose release from the liver during glucose infusions, secondary to a blunted hepatic insulin signaling. (21)(22) Insulin secretion in response to hyperglycemia is intact in most preterm infants. (14)(18) However, secretion of proinsulin, which is less potent than insulin by 10-fold, predominates. (21)

COMPLICATIONS

Animal Data

Hyperglycemia is associated with increased mortality and poor weight gain in preterm lambs. Key genes involved in pancreatic β-cell development and glucose sensing remain suppressed in young adulthood. (23) In preterm baboons corresponding in gestational age to human preterm infants born at 24 weeks' gestational age, hyperglycemia during the first 5 days after birth is associated with accelerated renal glomerular maturation and oxidative stress. (24) Sustained hyperglycemia in neonatal mice is associated with reduced angiogenesis, neuronal degeneration, and macrophage and microglial infiltration in the retina, a pathology similar to retinopathy of prematurity (ROP) in human infants. (25) Studies from our laboratory have demonstrated that hypoinsulinemic hyperglycemia in neonatal rats that are neurodevelopmentally equivalent to human extremely preterm infants causes oxidative stress; DNA damage; cytokine upregulation; microgliosis and astrocytosis in the cerebral cortex and hippocampus; and long-term impairments in hippocampal synaptogenesis, substrate utilization, and function. (26)

Human Data

Complications in the Neonatal Period. Hyperglycemia has been associated with increased risk of death, intraventricular hemorrhage (IVH), sepsis, necrotizing enterocolitis, ROP, and a longer length of hospital stay in extremely preterm infants. (3)(5)(6)(8)(11)(12)(13)(19)(27) A more severe and longer duration of hyperglycemia increases the risk of death and IVH, (8)(13)(27) though not all studies have found this effect; (5) 1 study reported a mortality rate as high as 40%. (13) Rapid changes in serum osmolarity are postulated as the cause of IVH. However, plasma osmolarity increases minimally during hyperglycemia, suggesting that other factors (eg, loss of autoregulation) may be involved. Moreover, as the brain accounts for the majority of glucose utilization in the body, hyperglycemia could be reflective of decreased glucose utilization in the injured brain. Hyperglycemia has also been associated with bacterial and fungal infections. Conversely, the counterregulatory hormonal (eg, catecholamines) response during sepsis could cause or worsen hyperglycemia. (19) Hyperglycemia on the first day after birth is a risk factor for reduced brain white matter content at term. (5) The association between hyperglycemia and ROP is inconsistent. (10)(28)(29) A meta-analysis of 9 studies involving 1,939 infants and 509 cases of ROP found no association between mean blood glucose concentrations and ROP (adjusted odd ratio [OR] = 1.08, P = .15) and a borderline significant association between duration of hyperglycemia and ROP (adjusted OR = 1.08, P = .03). (30)

Long-term Complications. Unlike the acute complications, data on long-term complications of hyperglycemia in extremely preterm infants are sparse. Associations between hyperglycemia in the neonatal period and long-term alterations in growth, body composition, neurodevelopment, and cardiovascular/metabolic health have been reported. In a group of infants born at less than 30 weeks' gestation or with a birthweight less than 1,500 g who developed hyperglycemia (defined as 2 consecutive blood glucose concentrations >153 mg/dL [>8.5 mmol/L] at least 4 hours apart), survival without neurodevelopmental abnormalities at school age was 37%. (31) However, this study did not have a control group without hyperglycemia. Another small retrospective case control study of 33 infants born at less than or equal to 32 weeks' gestational age found that those with hyperglycemia (defined as blood glucose concentration ≥180 mg/dL [≥10 mmol/L] during a 12-hour period) were more likely to have abnormal neurologic and behavioral development at 2 years' corrected age. (13) However, this study relied on a behavioral checklist and did not include standardized neurobehavioral testing. (13) Our study using standardized neurodevelopmental testing showed that VLBW preterm infants with hyperglycemia (defined as ≥1 blood glucose concentration >150 mg/dL [>8.3 mmol/L] in a day) for more than or equal to 5 days during the first 14 days after birth had significantly lower cognitive, motor, and language scores on the Bayley Scales of Infant Development III at 12 months' corrected age (unpublished data).

In addition to poor neurodevelopment, long-term alterations in growth have also been reported in VLBW preterm infants experiencing hyperglycemia in the neonatal period. Infants with hyperglycemia (≥1 blood glucose concentration >150 mg/dL [>8.3 mmol/L]) in a day) for more than or equal to 5 days during the first 14 days after birth were found to have decreased weight, length, and head circumference for up to 2 years' corrected age, and decreased adiposity for up to 4 months' corrected age. (7)(8) At 7 years of age, infants with hyperglycemia (2 consecutive blood glucose concentrations >153 mg/dL [>8.5 mmol/L] at least 4 hours apart) randomized to tight glycemia control (target blood glucose concentration, 72–108 mg/dL [4–6 mmol/L]), had similar weight and head circumference as those randomized to standard glycemia control (target blood glucose concentration, 144–180 mg/dL [8–10 mmol/L]), but were shorter and had higher fat-free mass. (31)

More recently, data were published on the long-term metabolic ramifications of neonatal hyperglycemia. Children with hyperglycemia in the neonatal period randomized to tight glycemia control were found to have lower fasting glucose concentrations at 7 years of age, but their glucose tolerance was otherwise similar to that of the children randomized to standard glycemia control. (31) In a group of 171 preterm infants born before 27 weeks' gestation, those who experienced hyperglycemia (defined as a blood glucose concentration >180 mg/dL [>10 mmol/L]) on 1 or more days during the first 28 days after birth were noted to have higher diastolic blood pressure at 6.5 years. (32) The risk increased with the severity and duration of hyperglycemia. Each additional day with 1 or more blood glucose concentrations greater than 252 mg/dL (>14 mmol/L) was associated with an approximately 0.5 SD increase in systolic and diastolic blood pressures at 6.5 years. (32)

The mechanisms behind these long-term alterations in growth, neurodevelopment, and metabolic health remain largely unknown. One possible mechanism is related to a decrease in nutrient intake as a consequence of the lowered glucose infusion as a treatment/prevention strategy for controlling the hyperglycemia. Decreased nutrient intake in the first weeks after birth has been associated with long-term alterations in growth, neurodevelopment, and metabolic health, potentially through the effect on the growth hormone axis. Our recent study showed that the associations between hyperglycemia and later growth and neurodevelopment diminished when the first-week nutrient intake was accounted for and differences were no longer significant (unpublished data). Insulin treatment may also potentially affect the growth hormone axis and thereby affect long-term outcomes. Finally, hyperglycemia is more common in infants who are more immature and critically ill. Therefore, hyperglycemia may be simply a marker of infants who are overall more unstable and at risk for poorer long-term outcomes. Randomized trials of varying strategies of nutrient provision and/or insulin therapy and long-term follow-up of growth, neurodevelopment, and metabolic health are needed to confirm these relationships, determine the underlying mechanisms, and improve clinical care and overall health for this vulnerable population.

Role of Glycemic Variation in Outcomes. There are concerns that glycemic variations may be more detrimental than hyperglycemia. In a group of VLBW infants, glycemic variation, but not mean glucose concentration, was associated with first-week mortality. (33) Likewise, VLBW infants with unstable glycemia (≥1 episode of hypoglycemia and hyperglycemia) in the first week were found to have lower odds of survival without neurodevelopmental impairment at 2 years. (11) Other studies have not found associations between glycemic variations and short- and long-term outcomes. (29)(34) As with hyperglycemia, glycemic variations are more likely in preterm infants who are more immature, smaller, and sicker, and these factors, rather than glycemic variations, could be responsible for the adverse outcomes. (11)

MANAGEMENT

Prevention

Higher protein intake in parenteral nutrition is associated with a reduction in the overall incidence of hyperglycemia in VLBW infants (typical relative risk = 0.69, 95% confidence interval = 0.49–0.96). (35) A daily amino acid intake of 4 g/kg per day decreases the odds of developing hyperglycemia by 67%, compared with an intake of 2.5 g/kg per day. (36) Improved insulin secretion is likely responsible for the beneficial effect of amino acids. Arginine and glutamine in particular appear to be important for glucose regulation. (37) A strictly controlled glucose infusion rate, higher parenteral fat intake, early initiation of enteral feeding, and faster achievement of full feeding decrease the risk for hyperglycemia. (12)(32)(38)(39) A Cochrane review in 2011 concluded that there is insufficient evidence to recommend lowering glucose infusion rates as a *prevention* strategy. (40) Likewise, use of insulin as a prevention strategy is not recommended. A multicenter trial of 195 VLBW infants demonstrated that a continuous insulin infusion at a dose of 0.05 units/kg per hour during the first week after birth lowered the risk for hyperglycemia but increased the risk for hypoglycemia and death before 28 days, compared with standard neonatal care. (41)

Treatment

Surveys of clinical directors of tertiary neonatal departments in Australia and New Zealand, and neonatal pharmacists and neonatologists in level 3 neonatal services in the United Kingdom indicate that all would treat hyperglycemia in extremely preterm infants, albeit at different glucose thresholds and using different approaches. (2)(42) Addressing the precipitating factors (pain, stress, sepsis, and medications) will help to some extent, but most extremely preterm infants with persistent hyperglycemia will require treatment.

Treatment Options. The 2 treatment options for VLBW infants with hyperglycemia are lowering the glucose infusion rate and administration of insulin. In a randomized trial of a small sample size (N=23), both strategies were equally effective in controlling hyperglycemia (82% with glucose reduction and 100% with insulin administration). (14) Typically, both strategies are used, with most neonatologists undertaking glucose reduction as the initial step. A survey of tertiary neonatal departments in Australia and New Zealand showed that 70% would decrease glucose intake and 30% would use insulin during the first 3 days after birth. The percentage of departments using these 2 strategies after 3 days was 57% and 43%, respectively. (2) A similar effect was found in a more recent study with very few infants having received insulin in the first week after birth and over 50% in the third and fourth weeks. (12)

The association between higher glucose infusion rates and risk for hyperglycemia supports reducing the glucose infusion rate as a treatment strategy. (4)(10)(20) A recent study demonstrating an association between higher carbohydrate intake during postnatal weeks 1 to 8 and higher blood pressure at 6.5 years also supports this approach. (32) The downside is risk of calorie deficit. In the aforementioned randomized trial, (14) infants treated using glucose reduction received less than 60 kcal/kg per day energy intake (resting energy expenditure) for a longer period than those treated using insulin, with some infants having received less than 60 kcal/kg per day for 2 weeks or more. Such prolonged calorie deficits could have detrimental effects on long-term growth, body composition, and neurodevelopment, as described earlier. (7)(9) It is prudent to maintain a glucose infusion rate of at least 6 mg/kg per minute to match the basal glucose requirement of extremely preterm infants. (43) Avoidance of fluctuations in the glucose infusion rate decreases the risk for hyperglycemia, (39) but is difficult to implement with intermittent glucose checks and manual adjustments in glucose infusion rates.

Use of insulin to treat hyperglycemia is associated with lower mortality in extremely preterm infants. (12) In addition to its role in glucose homeostasis, insulin is a growth factor in the fetal period. Insulin administration improves utilization of infused glucose better than suppression of endogenous glucose production, and thus, permits greater calorie intake. (14) Moreover, insulin decreases urinary glucose losses, thus leading to greater retention of infused glucose. (44) In randomized trials, insulin infusion was associated with better glucose tolerance, nonprotein energy intake, and weight gain, compared with reduction of glucose infusion. (14)(19) A more recent study showed that tight glycemic control in VLBW infants using insulin was associated with better weight gain and head growth up to 36 weeks' postmenstrual age, and lower fasting glucose concentrations at 7 years of age. (31)(44) However, linear growth was negatively affected. (31)(44)

The major concern with insulin use is the risk for hypoglycemia, though severe hypoglycemia (blood glucose concentration <40 mg/dL [<2.2 mmol/L]) is rare (∼1%). (19) A randomized trial targeting a blood glucose range of 72 to 108 mg/dL (4–8 mmol/L) using insulin showed that the incidence of hypoglycemia (defined as a blood glucose concentration <47 mg/dL [<2.6 mmol/L]) increased from 27% to 58%, relative to standard glycemic control (target blood glucose range, 144–180 mg/dL [8-10 mmol/L]). (44) However, this increased risk for hypoglycemia was not associated with adverse neurodevelopment at school age. (31) The other disadvantages of insulin use are the need for frequent glucose checks, frequent adjustments to the glucose infusion rate and insulin dosage, and the requirement of vascular access. (19)(44) Furthermore, the long-term effects of insulin treatment on growth and development are not well understood.

Insulin Dose and Target Glycemia. There is a wide variation in criteria used for starting insulin treatment. (2)(45) The typical starting dose is between 0.05 and 0.1 units/kg of regular insulin. Most neonatologists will initially administer a bolus and transition to a continuous infusion of 0.01 to 0.05 units/kg per hour if hyperglycemia persists. Preterm infants have a higher metabolic clearance rate of insulin than adults and thus may require higher insulin infusion rates. One study found that euglycemia could be achieved at a mean duration of 31.4 hours after starting insulin. (46) Others have reported using insulin for as long as 21 days. (19) Compared with a higher target glycemia range, a lower target requires a longer duration of administration. (44)

The optimal target glucose range in extremely preterm or VLBW infants is not known. A survey of clinical directors of tertiary neonatal departments in Australia and New Zealand indicated a wide range of target glucose concentrations, ranging from 54 to 144 mg/dL (3–8 mmol/L). (2) In a randomized trial of infants born before 30 weeks' gestation or with a birthweight less than 1,500 g, maintaining a blood glucose concentration between 72 and 108 mg/dL (4 and 6 mmol/L) was associated with better weight gain and head growth, but not linear growth, until 36 weeks' postmenstrual age, compared with maintenance of blood glucose concentration between 144 and 180 mg/dL (8 and 10 mmol/L). (44) There was no difference in nutritional intake, mortality, or neonatal morbidities between the 2 groups. Infants assigned to the lower glycemia range had more episodes of hypoglycemia, as described before. (44) Follow-up at school age showed that children in the tight glycemia group had a similar rate of survival without neurodevelopmental abnormalities as those in the standard glycemia group, but were approximately 4 cm shorter, had better height-adjusted lean mass, and had lower fasting blood glucose concentration. (31) Further exploratory analysis showed that the 72 to 108 mg/dL (4–6 mmol/L) blood glucose range in either group was associated with a greater chance of survival without neurodevelopmental impairments and better full-scale IQ at age 7 years. (31) However, tight glycemia control is difficult to achieve and labor-intensive.

Role of CGM in the Management of Hyperglycemia

In addition to being labor-intensive, intermittent blood glucose checks do not provide a true picture of glycemic variations in extremely preterm infants. Such measurements also lead to selection bias because infants with abnormal glucose concentrations are likely to be monitored more frequently than those found to have a normal glucose concentration. CGM using a subcutaneous glucose sensor overcomes both of these limitations. A study in 188 VLBW infants showed that CGM data correlate well with point-of-care glucose measurements (R=0.94) during the first week after birth. (47) The sensitivity of CGM to detect hyperglycemia was 88%; specificity, 98%; positive predictive value, 90%; and negative predictive value, 98%. (47) CGM coupled with computer-assisted adjustments in glucose/insulin infusion increases the time spent in the euglycemia range and reduces glycemic variability and duration of hyperglycemia in VLBW infants, compared with glucose control based on intermittent glucose measurements. (48)(49) A recently published randomized trial has demonstrated the feasibility of closed-loop insulin delivery guided by CGM in preterm infants with birthweights less than 1,200 g. (50) A control algorithm aimed at maintaining blood glucose between 72 and 144 mg/dL (4 and 8 mmol/L) calculated the insulin dose and dextrose infusion rate. Infants treated using the closed-loop system spent more time in target glycemia range than those in whom a paper algorithm-guided strategy was used (91% vs 26%, P<.001). (50) However, this study has several limitations; the sample size was small (N=10 per group), the observation period was short (24 hours), and adjustments to insulin and dextrose infusions were not based on real-time glucose concentrations and not automated. (50) Nevertheless, the results are promising and warrant additional studies. It should be noted that CGM has not been approved for use in newborn infants and its use should be considered investigational at present.

CONCLUSION

Hyperglycemia is common in extremely preterm infants and is associated with adverse short- and long-term outcomes. The pathogenesis is multifactorial and treatment strategies remain varied. Although decreasing the glucose infusion rate is a common strategy for prevention and treatment, this strategy likely contributes to poorer long-term growth and neurodevelopmental outcomes. Further research is needed to determine the optimal management strategy for hyperglycemia in this vulnerable population.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes, including genetic disorders and other clinical conditions, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the clinical and laboratory features and approach to therapy of neonatal hyperglycemia, including transient diabetes mellitus.

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NeoReviews Quiz

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1. Hyperglycemia is a common problem in very-low-birthweight (VLBW) infants and is associated with adverse short- and long-term outcomes. Which of the following statements regarding hyperglycemia in VLBW infants is correct?
   - A. Hyperglycemia is defined as a blood glucose concentration greater than 125 mg/dL (>7 mmol/L) because it corresponds to the renal glucose threshold in VLBW infants.
   - B. Glucose levels peak within the first 48 hours after birth.
   - C. Hyperglycemia typically resolves by the end of 72 hours after birth.
   - D. Studies using continuous glucose monitoring (CGM) indicate that hyperglycemia occurs in up to 80% of VLBW infants.
   - E. Severe hyperglycemia (>180 mg/dL [>10 mmol/L]) for greater than 10% of the time occurs in 50% of VLBW infants during the first week after birth.
2. The risk for hyperglycemia is inversely correlated to gestational age and birthweight. Other risk factors for the development of hyperglycemia have been identified. Which of the following statements does NOT represent a risk factor for hyperglycemia in VLBW infants?
   - A. Need for vasoactive medications.
   - B. A glucose infusion rate greater than 6 mg/kg per minute.
   - C. Higher protein intake.
   - D. Longer duration of parenteral nutrition.
   - E. Exposure to corticosteroids.
3. VLBW infants with hyperglycemia are at increased risk for short- and long-term complications. Which of the following complications has NOT been associated with neonatal hyperglycemia?
   - A. Necrotizing enterocolitis.
   - B. Hemodynamically significant patent ductus arteriosus.
   - C. Intraventricular hemorrhage.
   - D. Increased risk for hypertension in childhood.
   - E. Decreased weight at age 2 years.
4. Treatment strategies for VLBW infants with hyperglycemia include decreasing the glucose infusion rate and insulin therapy. Which of the following statements regarding the use of insulin for the treatment of hyperglycemia in VLBW infants is correct?
   - A. The use of insulin to treat hyperglycemia is associated with increased mortality.
   - B. The use of insulin to treat neonatal hyperglycemia is associated with improved linear growth at age 7 years.
   - C. Treatment with insulin has not been shown to improve head growth.
   - D. The improved weight gain noted in neonates treated with insulin for hyperglycemia is no longer observed at 36 weeks' postmenstrual age.
   - E. VLBW infants who receive insulin for hyperglycemia have lower fasting glucose concentrations at age 7 years.
5. CGM is an alternative to intermittent blood glucose checks. Which of the following statements regarding the use of CGM for hyperglycemia management is false?
   - A. CGM relies on the measurement of glucose in subcutaneous tissues.
   - B. CGM is highly correlated with point-of-care glucose measurements (R=0.94).
   - C. Both the sensitivity and specificity of CGM are above 90% for the detection of hyperglycemia.
   - D. The negative predictive value of CGM to detect hyperglycemia is 98%.
   - E. Closed-loop delivery of insulin guided by CGM has recently been shown to be feasible in preterm infants weighing less than 1,200 g.

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Updates on Assessment and Monitoring of the Postnatal Growth of Preterm Infants

Erika G. Cordova, MD,* Mandy Brown Belfort, MD, MPH†

*Department of Medicine, Boston Children's Hospital, Boston, MA

†Department of Pediatric Newborn Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Education Gaps

1. Several growth curves for preterm infants were developed in the past decade. To use them effectively, clinicians need to understand the methods and sample populations used in their development, and the strengths and limitations of each.
2. Percentiles and *z* scores are used to compare an infant's size to an external reference or standard. To diagnose growth alterations, the *z* score change over time is more useful than the percentile or *z* score at a single time point.
3. Body mass index curves are now available to monitor the proportionality of preterm postnatal growth and offer the potential to promote a healthier body composition in preterm infants.

Abstract

Assessing and monitoring the physical growth of preterm infants is fundamental to NICU care. The goals of nutritional care are to approximate the growth and body composition of the healthy fetus and to support optimal brain development while minimizing future cardiometabolic risk. Both poor and excessive growth predict adverse long-term health outcomes. Growth curves are clinical tools used to assess the preterm infant's growth status. Several growth curves for preterm infants were developed in the past decade. To use them effectively, clinicians need to understand how each growth curve was developed; the underlying reference population; intended use; and strengths and limitations. *Intrauterine growth curves* are references that use size at birth to represent healthy fetal growth. These curves serve 2 purposes—to assign size classifications at birth and to monitor postnatal growth. The *INTERGROWTH-21st preterm postnatal growth standards* were developed to compare the postnatal growth of preterm infants to that of healthy preterm infants rather than the fetus. *Individualized weight growth curves* account for the water weight loss that frequently occurs after birth. In addition, *body mass index (BMI) curves* are now available. In this review, we discuss the main characteristics of growth curves used for preterm infants as well as the use of percentiles, *z* scores, and their change over time to evaluate size and growth status. We also review the differences in body composition between preterm infants at term-equivalent age and term-born infants and the potential role of monitoring proportionality of growth using BMI curves.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
BMI	body mass index
EUGR	extrauterine growth restriction
IUGR	intrauterine growth restriction
LGA	large for gestational age
SD	standard deviation
SGA	small for gestational age
VON	Vermont Oxford Network
WHO	World Health Organization

Objectives After completing this article, the readers should be able to:

1. Identify the main characteristics, strengths, and limitations of the growth curves—references and standards—available to monitor the postnatal growth of preterm infants.
2. Recognize the role of percentiles, z scores, and z score change in the assessment and monitoring of preterm growth status.
3. Describe the differences in body composition between preterm infants at term-equivalent age and term-born infants, and the potential role of monitoring proportionality of growth using recently available body mass index curves.

BACKGROUND

The third trimester of pregnancy is a period of rapid fetal growth and development. Normal fetal growth is abruptly interrupted at the time of premature birth. How the fetus grows in utero and how the preterm infant grows postnatally both influence long-term health. (1) Some studies suggest impaired fetal growth (termed "intrauterine growth restriction" IUGR]) as well as impaired postnatal growth (termed "extrauterine growth restriction" [EUGR]) are associated with higher mortality and adverse long-term neurodevelopmental outcomes among survivors. (2)(3) However, excessive postnatal weight gain has been associated with a heightened risk for cardiometabolic disease later in life. (4)(5) The current recommendation of the American Academy of Pediatrics (AAP) is for preterm infants "to achieve postnatal growth and body composition equivalent to those of normally growing, healthy human fetuses of the same gestational age." (6) Although the *ideal* pattern of growth for preterm infants remains undefined, the desirable goal is to avoid both poor and excessive growth.

Growth curves are the clinical tools used to assess and monitor the adequacy of preterm infants' growth status. Several growth curves for preterm infants were developed over the past decade. These growth curves differ in the methodology used in their creation, their intended use, and the characteristics of the preterm infants that contributed to them. In addition, the curves were developed as either references or standards. References describe how a fetal population *grew* at a specific location and period and align with the reference fetus concept underlying the AAP recommendation. In contrast, a recently published standard is intended to prescribe how preterm infants *should grow*, given optimal conditions, but is not grounded in the reference fetus concept. (7) To assess and monitor growth in the NICU, an infant's anthropometric measurement is plotted against a growth curve. The result of this assessment is a specific percentile or Z score, which represents the infant's size *relative* to the external references or standard selected. Therefore, it is important for clinicians to understand how a set of growth curves was created in order to choose the growth curve that best fits their purpose and clinical setting.

The clinical use of growth curves encompasses the assessment of size at birth, the longitudinal monitoring of postnatal growth, and the assessment of size at hospital discharge or term-equivalent age. From the infant's size at birth, the clinician can make an inference about fetal growth. Fetal growth is influenced by maternal health and fetal and placental factors. (8) Categorization of size alterations at birth—IUGR and small for gestational age (SGA) or large for gestational age (LGA)—allows clinicians to identify preterm infants at heightened risk for neonatal morbidities such as hypoglycemia and necrotizing enterocolitis. (9) SGA and IUGR are distinct entities. Infants born SGA (defined as weight <10th percentile for gestational age) may have grown appropriately based on their genetic potential or may be pathologically small. In contrast, IUGR is a pathologic process that implies that the fetus did not reach its growth potential because of genetic or environmental factors. SGA is a classification of size at a single time point—birth—whereas the diagnosis of IUGR requires serial assessments over time during pregnancy. (10) A fetus diagnosed as IUGR may not be classified as SGA at birth, and a preterm infant categorized as SGA at birth may not be IUGR. After birth, the postnatal growth of preterm infants is influenced by both nutritional and non-nutritional factors. Characterization of the postnatal growth status, including poor or excessive growth, as well as classification of size at NICU discharge or term-equivalent age also serves as an indicator of long-term morbidity risk. (11) Failure to identify and manage growth alterations can contribute to poor outcomes, whereas targeted interventions to improve growth in the NICU can improve long-term outcomes.

To optimize the long-term health of preterm infants, it is important to promote healthy physical growth, including the accumulation of healthy levels of body fat and lean mass. Despite advances in neonatal nutritional care, preterm infants at term-equivalent age have a different body composition than term-born infants. The body composition of preterm infants is characterized by less lean tissue and more adipose tissue than their term counterparts. Newer technologies exist to directly estimate fat-free mass and fat mass. However, until direct measurement of body composition becomes routine practice in the NICU, monitoring proportionality indexes such as body mass index (BMI) is highly feasible and has the potential to help clinicians support healthier preterm growth. In this review, we will summarize the main characteristics, strengths, and limitations of the growth curves available to assess and monitor the postnatal growth of preterm infants. We will further develop the concept of percentiles and *z* scores, and the role of growth trajectories to evaluate preterm growth status, highlighting areas for future research. Finally, we will review the differences in body composition between preterm infants at term-equivalent age and term-born infants, and the potential role of monitoring proportionality of growth using BMI curves.

GROWTH CURVES USED FOR ASSESSMENT OF PRETERM INFANTS

Growth curves are the clinical tools used to assess and monitor the growth of preterm infants at birth and in the postnatal period. Plotting an infant's growth on a standardized growth curve provides an assessment of whether and if so, how far an infant is deviating from his/her target growth. (10) The concept of *target growth* is important because it represents the growth goal. Deviations from the target growth (upward or downward) are considered "abnormal" and warrant clinical investigation and intervention.

Growth curves are developed as either references or standards. By definition, *references* constitute descriptive tools. References describe newborn size across the range of gestational ages to provide information about how a fetal population *grew* at a specific location and period. The data used in growth references is often derived from samples that include both low- and high-risk pregnancies affected by pathologic processes that can affect fetal growth (eg, preeclampsia, maternal diabetes). The anthropometrics used for the construction of references are typically clinical measures obtained from medical records, which are subject to error, particularly for length and head circumference. In contrast, growth *standards* are prescriptive tools. Standards are intended to represent how preterm infants should grow if born to healthy mothers with uncomplicated pregnancies and having optimal neonatal-perinatal conditions, aside from their premature birth. Infants exposed in utero or postnatally to pathologies that can affect growth are excluded, leaving a sample of "healthy" preterm infants. (12) In addition, the anthropometric measurements used in the construction of existing standards are obtained following standardized procedures and quality control measures to minimize error.

Many intrauterine growth references, 1 set of preterm size-at-birth standards and 1 set of preterm postnatal growth standards are currently available. The main characteristics of the preterm growth curves, such as references and standards, discussed herein are summarized in the Table.

Intrauterine Growth Curves

Intrauterine growth curves are also called size-at-birth or fetal charts because they use the size at birth of preterm infants born at different gestational ages as a proxy for fetal growth. A few intrauterine growth references and 1 set of intrauterine standards have been published. The intrauterine growth references are published elsewhere. (13)(14)(15)(16)(17) The curves published in 2015 by the INTERGROWTH-21st consortium include a set of standards (the neonatal size-at-birth charts) and a set of references (the very preterm size-at-birth charts). Intrauterine growth curves can be used for 3 purposes: 1) to assess growth status at birth and assign size classifications of SGA, appropriate for gestational age, and LGA, 2) to monitor longitudinal growth of preterm infants, and 3) to assess for EUGR at NICU discharge or term-equivalent age.

Intrauterine Growth References. The intrauterine growth references use size at birth as a proxy for the recommended growth target: the healthy fetal size, also known as the reference fetus. These curves were constructed by using cross-sectional measurements of the size at birth of a large number of infants across the range of gestational ages.

In 2010, Olsen et al published intrauterine growth curves using a large administrative dataset in the United States. (13)

TABLE. **Comparison of Preterm Growth Curves Available to Monitor the Postnatal Growth of Preterm Infants**

	OLSEN ET AL (13)(14)[a]		FENTON AND KIM (15)		BOGHOSSIAN ET AL (16)	ARIS (17)	INTERGROWTH-21ST SIZE AT BIRTH CHARTS (28)	INTERGROWTH-21ST VERY PRETERM SIZE AT BIRTH CHARTS (26)	INTERGROWTH-21ST PRETERM POSTNATAL GROWTH STANDARDS (28)	
Aim	Descriptive Reference		Descriptive Reference		Descriptive Reference	Descriptive reference	Prescriptive Standard	Descriptive Reference	Prescriptive Standard	
Method	Administrative dataset		Systematic review and meta-analysis of 6 datasets		Administrative dataset	2017 natality dataset	International multicenter prospective study with strict selection of low-risk pregnancies without impaired fetal growth			
	Cross-sectional measures of size at birth								Postnatal repeated longitudinal measures	
Anthropometric measurements	Clinical data		Clinical data		Clinical data	Birth certificate data	Standardized data			
Location of data	248 US hospitals in 33 states		Germany, United States, Italy, Australia, Scotland, and Canada		852 US centers of VON	United States	Brazil, Italy, Oman, United Kingdom, United States, China, India, and Kenya			
Years of data collection	1998–2006		1991–2007		2006–2014	2017	2009–2014			
Gestational age at birth	23–41 weeks		22–40 weeks		22–29 weeks	22–42 weeks	33–43 weeks	24–32 weeks	27–37 weeks	
Gestational age estimation	By neonatologist best estimate[b]		First-trimester ultrasound, maternal dates and/or infant assessment		As defined in VON manual[c]	Best obstetric estimates	Ultrasound before 14 weeks' pregnancy			
Age accuracy	Completed weeks		Weeks and days		Weeks and days	Completed weeks	Completed weeks	Completed weeks	Completed weeks	
Sample size by gestational age	<37 weeks	<32 weeks	<37 weeks	<32 weeks	22–19 weeks	22–37 weeks	33–37 weeks	24–32 weeks	<37 weeks	<32 weeks
Weight (No.)	257,855	12,011	3,986,456	58,484	156,587	257,026	1,022	408	201	12
Length (No.)	257,855	12,011	175,573	23,802	—	—	1,014	408	201	12
Head circumference (No.)	257,855	12,011	175,573	23,802	156,587	—	1,016	408	201	12
BMI[a] (No.)	254,454	11,630								
Additional features	Infants admitted to the NICU who survived		Smoothing of curves from 36 to 50 weeks Includes Olsen population		Race-specific charts were generated from a subgroup of infants	Excluded mothers <18 years old	Infant and maternal factors for fetal growth restriction excluded	Some fetal growth restriction factors (except smoking or severe obesity)	Infant and maternal factors for fetal growth restriction excluded	
Online sources	www.pediatrix.com/ workfiles/NICUGrowth Curves7.30.pdf		www.ucalgary. ca/fenton/ 2013chart			https://izzuddin-aris.shinyapps.io/BW-for-GA_z-score_webapp/	www.intergrowth21.org.uk/			

BMI=body mass index; VON=Vermont Oxford Network; —=no data available.

[a] *Olsen BMI curves for preterm infants.*

[b] *Using obstetric history, obstetric examinations, prenatal ultrasonography, and postnatal physical examinations.*

[c] *Obstetrical measures based on last menstrual period and prenatal ultrasonography in the maternal chart or, if unavailable, a neonatologist's estimate based on postnatal physical examinations.*

The dataset included anthropometric measurements collected on more than 250,000 infants born at 22 to 41 weeks' gestation at 248 US hospitals. The authors developed sex-specific smoothed curves for birthweight, length, and head circumference for gestational age in completed weeks. The Olsen curves were updated to also display the World Health Organization (WHO) child growth standards from 41 to 50 weeks' postmenstrual age. In 2015, Olsen and colleagues published the first set of sex-specific BMI curves for preterm infants based on the same dataset used to create the Olsen 2010 growth references for weight, length, and head circumference. (14) These intrauterine BMI curves can be used to identify and quantify disproportionate preterm growth in the NICU, however, the extent to which different BMI patterns of growth predict short- and long-term outcomes has not yet been well studied.

In 2013, Fenton and Kim conducted a systematic review and meta-analysis to combine the data from 6 population-based studies from developed countries including the dataset used by Olsen. (15) The anthropometric measurements from almost 4 million infants born at 22 to 40 weeks' gestation were incorporated in the sex-specific curves for weight, length, and head circumference. Of note, different populations were used to develop the weight curves and the head circumference/length curves. In contrast to the Olsen curves, the x-axis of the revised Fenton curves shows actual gestational age in weeks and days (vs completed weeks). In addition, a unique feature of the Fenton curve is the statistical smoothing from 36 to 50 weeks' postmenstrual age as it links to the WHO standards for term infants. The authors compared their fetal growth curves with the postnatal longitudinal growth curves derived from 977 preterm infants who were followed from birth until 50 weeks' postmenstrual age (PreM growth study). (18) They noted a disjuncture between the fetal and the longitudinal preterm growth curves around 40 weeks' gestation. The fetal curves displayed a slight downward trajectory between 37 and 40 weeks' postmenstrual age whereas preterm infant curves showed a continued upward trajectory during this period. The authors then made a number of statistical assumptions to graphically connect their fetal growth curves with the WHO infant curves. By doing so, the slope of their percentiles between 37 and 40 weeks' postmenstrual age increased to align with the WHO percentiles at 50 weeks. The "smoothed slopes" followed the same trajectory as the longitudinal preterm infant growth of the PreM growth study. (18)

In 2016, Boghossian and colleagues published new preterm growth curves for birthweight and head circumference for infants born at 22 to 29 weeks' gestation. (16) The curves were developed using data from inborn, singleton infants from 852 US centers of the Vermont Oxford Network (VON). The sample of infants that contributed to the curves was more recent than the samples used by Olsen (13) and Fenton and colleagues, (18) which allowed for the inclusion of a greater number of infants born at 22 and 23 weeks' gestation. Compared with the Olsen intrauterine growth curves, (13) the Boghossian curves are shifted downward but the absolute differences between the 2 sets of curves is small. The systematic difference between the curves is likely related to the inclusion of younger infants (22–23 weeks' gestation) in the sample population used by Boghossian et al. (19) A secondary aim of the investigators was to generate sex- and race-specific curves for black, white, and Asian infants. For most gestational ages, the predicted percentiles for birthweight for black infants were lower compared with white and Asian infants. These results reflect the over-representation of black infants at lower gestational ages (34% of black infants born at 22 to 29 weeks' gestation in VON vs 16% of black infants of all gestational ages in the United States). We do not advocate for the use of race/ethnicity–specific growth references. Whereas sex is a fixed trait, differences in birth size by race/ethnicity often reflect modifiable disparities in maternal social and environmental factors and/or obstetrical care. (20) In addition, differences in postnatal growth may reflect race- or ethnicity-based disparities in NICU care for infants. (21)

In 2019, Aris et al published an updated birthweight-for-gestational age reference using the nationwide 2017 US natality dataset. (17) The authors incorporated cross-sectional data from over 3 million birthweights from singleton live births, of which 7.5% were preterm at 22 to 37 weeks' gestation. Previous US birthweight-for-gestational-age references used the last menstrual period to estimate gestational age. By contrast, the updated reference used more accurate obstetric estimates of gestational age. In addition, this reference reflects the current sociodemographic composition of the United States. Aris et al also developed a website (Table) to calculate sex- or parity-specific continuous measures of birth size (eg, birthweight-for gestational age z scores). (17) However, this contemporary reference is limited to weight only.

Clinicians should recognize that using intrauterine growth references to monitor the postnatal growth of preterm infants has limitations. This approach assumes that fetuses were growing "healthily" up until the time they were born when, in reality, the factors that contribute to premature birth can adversely influence the size at birth. (22) By using the size at birth as a proxy for fetal size, there is a selection bias favoring lower weights. (10) The bias is somewhat mitigated by using very large datasets derived from developed countries where infant and maternal factors that may constrain fetal growth are minimized. One could argue that if the fetal size is the recommended *target growth*, an alternative approach could be to use growth curves developed by using ultrasound-based fetal measurements during pregnancy. Such fetal growth curves exist. (23) However, determination of fetal weight using ultrasonography is only an estimation of actual weight so it is subject to measurement errors. In addition, it is challenging to estimate fetal length using ultrasonography, and linear growth is an important component of preterm postnatal growth. (24) Consequently, intrauterine growth curves using the size at birth of preterm infants born at different gestational ages, rather than ultrasound-based size estimates, remain the most accepted estimate of "healthy" fetal size, which aligns with the current AAP recommendation and supports its use for monitoring preterm postnatal growth in clinical practice.

INTERGROWTH-21st Size-at-Birth Standards and References. The purpose of the INTERGROWTH-21st study was to develop international fetal and neonatal size and growth standards. To accomplish this goal, the INTERGROWTH-21st group conducted a series of projects following the WHO prescriptive approach used to construct the WHO child growth standards for term infants. (25) The INTERGROWTH-21st size-at-birth curves were published in 2015 and include a set of standards for infants born at 33 to 37 weeks' gestation and a set of references for preterm infants born at 24 to 32 weeks' gestation derived from a slightly different population. The size-at-birth standards were developed from the INTERGROWTH-21st Newborn Cross-Sectional Study. The investigators included healthy pregnant women with low risk for impaired fetal growth and measured the size of their newborns within 12 hours from birth. They published international sex-specific curves for birthweight, length, and head circumference by gestational age. The INTERGROWTH-21st size-at-birth curves include data collected from a sample of about 1,000 infants. The curves start at 33 weeks' gestation and complement the WHO growth standards at 42 weeks' postmenstrual age. (26) Because of the strict cohort selection criteria, the number of preterm births, particularly extremely preterm births, was very small. For this reason, the INTERGROWTH-21st investigators supplemented the original cohort with infants (n=408) born to mothers with some risk factors for impaired fetal growth (except smoking and severe maternal obesity) and published very preterm size-at-birth curves that start at 24 weeks' gestation. (27) The resulting curves are considered *references* (not standards) because at the lowest gestational ages, most pregnancies have some risk factors and postnatal practices are less standardized.

The aim of the INTERGROWTH-21st size-at-birth curves is to provide international standards for size-at-birth classification independent of racial/ethnic origin or geographical location. The authors of the INTERGROWTH-21st study do not support the use of size-at-birth curves for the purpose of longitudinal postnatal growth monitoring. They argue that the static evaluation of size at birth (representing growth in utero) and the longitudinal preterm growth are 2 distinct biological entities that should be evaluated using different clinical tools. (12)

Preterm Postnatal Growth Standards

The INTERGROWTH-21st preterm postnatal growth curves are based on a new concept: the growth target for the postnatal growth of preterm infants should be the growth of "healthy" preterm infants rather than the fetus. (12) This new concept challenges the currently recommended *reference fetus* on the grounds that hospitalized preterm infants and their postnatal environment cannot be compared to healthy fetuses that remained in utero. Therefore, attempting to match the growth of the healthy fetus is unattainable and could lead to detrimental cardiometabolic consequences later in life. (28) The preterm postnatal growth curves were developed as standards. The curves were constructed using repeated measures taken prospectively from a cohort of "healthy" preterm infants. The INTERGROWTH-21st cohort from which the sample was obtained followed strict selection criteria to include low-risk healthy pregnant women who had reliable pregnancy dating based on first-trimester ultrasonography (n=4,607). All live singletons from this cohort who were born between 26 and 37 weeks' gestation (n=201) were eligible for the preterm postnatal follow-up study that generated the final preterm postnatal growth curves. (29) The prospective design of the study allowed for the exclusion of infants exposed to perinatal factors that may affect fetal growth (eg, preeclampsia, maternal diabetes). (30) After birth, the preterm infants in the final cohort received evidence-based care including predominant feedings with fortified human milk. Infants who developed complications, such as necrotizing enterocolitis, chronic lung disease, sepsis, or any other postnatal condition that could affect growth, were excluded. (29)

Notably, the curves of the preterm postnatal standards are lower than the intrauterine growth curves, with the largest differences observed for infants born at lower gestational ages. (12) As expected, a recent study demonstrated that assessing growth with the INTERGROWTH-21st preterm postnatal standards reduced the diagnosis of EUGR (defined as weight below the 10th percentile at 36 weeks' postmenstrual age) compared with the assessment of EUGR using the Fenton and Kim 2013 growth reference. (15) Only 1 of every 5 cases categorized as EUGR based on the Fenton and Kim reference was categorized as normal according to INTERGROWTH-21st standards. (31) In other words, fewer infants were diagnosed with EUGR using the INTERGROWTH-21st standards than with the Fenton and Kim standard. (15) Clinicians should recognize that the selection of a specific growth reference or standard influences their growth assessments. (7) The main limitation of the preterm postnatal growth standards is that only a small number of infants born before 33 weeks' gestation contributed to the curves (n=12), which potentially limits their validity. The impact of using the preterm postnatal growth curves to monitor preterm postnatal growth, particularly at the youngest gestational ages, requires further research.

Individualized Growth Trajectories

Both intrauterine growth curves and preterm postnatal growth standards are limited by the fact that postnatal weight loss is not represented in the curves. The postnatal weight loss is due mainly to extracellular volume contraction. (32) Rochow and colleagues investigated this phenomenon in a multicenter, longitudinal study including preterm infants born at 25 to 34 weeks' gestational age who had uncomplicated postnatal courses. (33) The authors reported that healthy preterm infants consistently adjust their postnatal weight trajectory to a "new" trajectory that is on average 0.8 *z* scores below their birthweight percentile and largely represents extracellular volume contraction. The postnatal downshift from the birth growth percentiles is frequent and independent of gestational age. This concept prompted the development of individualized growth trajectories. (34) Similar to the intrauterine references, the approach for the development of the individualized growth trajectories follows the recommended fetal reference. However, the individualized curves incorporate typical weight loss that occurs after birth. After the postnatal adaptation is completed 21 days after birth, the individualized trajectories use corrected day-specific Fenton median growth velocities to continue the curves until 42 weeks' postmenstrual age when preterm infants are supposed to attain the weight and body composition of a healthy term infant as represented in the WHO child growth standards. Importantly, the authors also investigated the body composition in a subgroup of 20 healthy preterm infants. Compared with 2 other approaches tested for the development of the curves, Rochow et al (33) found that the infants who followed the individualized growth trajectories had the lowest values of fat mass percentage for their corresponding weight at term-equivalent age. The individualized growth trajectories are available at https://www.growthcalculator.org. They are sex-specific and provide day-specific target weights. The curves do not include length or head trajectories. Further research is needed to evaluate the ability of the reference based on individualized growth trajectories to predict long-term health outcomes of preterm infants.

Regardless of the preterm growth curve selected before term postmenstrual age, the consensus is to transition to the WHO growth standards at 42 weeks' postmenstrual age. The WHO curves are considered the standards for monitoring the longitudinal growth of children from birth to 24 months. (25)

USING GROWTH CURVES TO ASSESS POSTNATAL GROWTH OF PRETERM INFANTS

When monitoring the postnatal growth of preterm infants, clinicians make assessments of an infant's growth status. These assessments provide information about the infant's current health status as well as the child's future morbidity risk. (10) The components of a growth assessment include whether an infant's growth is "normal" or "abnormal" and if so, what is the direction of the growth alteration (poor or excessive growth) and what is the degree of the abnormality. Importantly, the identification of "abnormal" growth will depend on the external reference/standards that we choose to call "normal." We discuss the different approaches to growth assessments.

Percentiles

Percentiles and *z* scores are assigned to an anthropometric measurement (ie, weight, length, head circumference, or BMI) to represent the status of an infant's size for age relative to a reference population. As described previously, different growth curves use different references, for example, intrauterine growth curves use the fetus, whereas the preterm postnatal standard uses the healthy preterm infant. The percentiles and *z* scores associated with a measurement are influenced by the methodology and population underlying the development of the growth reference or standard selected. (7)(35)

Percentiles are essentially the rank position of an individual in a population and can be used to define the category in which the infant's size for age falls (eg, <10th percentile for SGA and >90th percentile for LGA). Compared with *z* scores, percentiles are intuitively more understandable and easier to use in clinical settings. They reflect an expected prevalence; for example, in a given population, 10% of infants are expected to fall at or below the 10th percentile. A limitation of using percentiles is that extreme values are lumped to the lowest/highest percentile. For instance, the weights of 2 infants who are below the first percentile at birth can correspond to very different absolute values. (35)

Z scores

Z scores are determined by using the distribution of the reference population. The *z* score for an anthropometric measure indicates how far and in what direction the observed value deviates from a central value of the reference population (eg, mean or median). It is expressed in units of the population standard deviation (SD). (36) *Z* scores are continuous variables, with values that can be negative, equal to zero, or positive. A negative *z* score means the observed value is below the central value of the population (eg, the 10th percentile corresponds to a *z* score of −1.28) whereas a positive *z* score means the observed value is above the central value (eg, the 90th percentile corresponds to a *z* score of 1.28). A *z* score of zero indicates that the observed value is equal to the mean of the reference population. (37) Compared to percentiles, *z* scores allow clinicians to quantify the degree of "abnormal" growth, which is particularly useful for values that fall outside percentile ranges. (38) For instance, 2 infants are born at 37 weeks' postmenstrual age, and infant A has a weight of 2,100 g and infant B has a weight of 1,800 g. Both infants rank below the third percentile for weight for age. However, infant A has a *z* score of −1.98 and infant B has a *z* score of −2.73, thus allowing for quantification of the degree of their growth failure. Because of these advantages, various growth references/standards are now accompanied by online calculators that allow clinicians to estimate age- and sex-specific *z* scores (Table).

Longitudinal Growth Monitoring

The primary purpose of monitoring the postnatal growth of preterm infants is the timely detection of growth alterations (eg, decline or acceleration in growth status) to adjust nutritional support. Failure to diagnose and treat growth alterations can contribute to poor outcomes, whereas targeted interventions to improve growth can improve outcomes. How the fetus grows in utero and how the preterm infant grows postnatally both influence long-term health. Therefore, assessing growth over time provides the most valuable clinical information because it incorporates the size at birth, representing fetal growth, *and* the size at a later time point, representing postnatal growth. In this context, the traditional definition of EUGR (ie, postnatal weight below the 10th percentile) has 2 important limitations. First, it is a cross-sectional assessment of *size* measured at a single time point rather than a longitudinal assessment of *growth* over time. (39)(40)(41) Second, it is typically measured at term-equivalent age or NICU discharge. Therefore, it fails to consider the growth that happened in utero, which is represented by the size at birth. As a result, infants with lower birthweights are more likely to be classified as having EUGR when they leave the NICU. For example, an infant who starts at the first percentile at birth (SGA) but grows appropriately during the NICU hospitalization to the ninth percentile at term-equivalent age, would be classified as EUGR even though the infant's weight for age increased by 9 percentiles postnatally.

To overcome the limitations noted before, clinicians can use growth trajectories for the longitudinal monitoring of postnatal growth. Growth trajectories are assessments of the change in size between 2 time points (eg, birth and NICU discharge). Therefore, they represent change in growth over time. A growth trajectory is represented by the *z* score change. *Z* scores are used instead of percentiles because *z* scores can be treated as continuous variables. A positive *z* score change indicates an increase in growth status while a negative *z* score change indicates a decline in growth status. A *z* score change of zero means that the growth status is stable or unchanged and that the infant is growing along his/her curve. (7) In addition, the *z* score change has better predictive ability for long-term outcomes than cross-sectional assessments of size. (42)(43)(44)(45) For these reasons, the *z* score change over time is preferable to the assessment of the specific *z* score or percentile measured at a single time point. Accordingly, recent guidelines recommend the use of the *z* score change in weight, length, and head circumference as primary indicators to identify and document neonatal malnutrition. (46) Importantly, when using *z* score change to categorize postnatal growth failure, one must select a cutoff under which the decline in *z* score from birth is considered to be "abnormal" (eg, too much or too little). Various cutoffs have been suggested in the literature. As an example, a decline in weight-for-age *z* score greater than 0.8 SD from birth is considered abnormal based on the individualized growth trajectories discussed earlier. Further research is needed to determine the impact of different preterm growth trajectories and cutoff values on meaningful short- and long-term outcomes.

BMI AND BODY COMPOSITION OF PRETERM INFANTS AT TERM-EQUIVALENT AGE

Even though the AAP recommendation for preterm growth was formulated over 4 decades ago, it already highlighted the importance of the *composition* of the growth attained. (6) Despite improvements in neonatal nutritional practices, preterm infants at term-equivalent age have a body composition

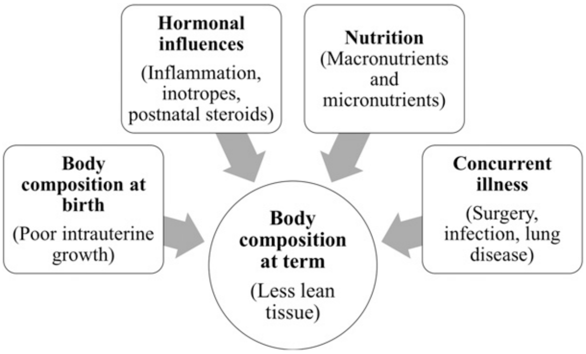
Hormonal influences
(Inflammation, inotropes, postnatal steroids)
Nutrition
(Macronutrients and micronutrients)
Body composition at birth
(Poor intrauterine growth)
Body composition at term
(Less lean tissue)
Concurrent illness
(Surgery, infection, lung disease)

Figure. Potential mechanisms underlying the altered body composition of preterm infants when they reach term-equivalent age.

that is different from healthy infants born at term, with substantially less lean body mass and a higher fat mass percentage. (47) The evidence suggests that excessive postnatal weight gain can be driven by excessive fat accumulation, which is associated with a negative metabolic and cardiovascular profile later in life. (48)(49)(50) In addition, the youngest preterm infants tend to have more visceral and overall adiposity at term-equivalent age than preterm infants of higher gestational ages. (51)(52) Recent anthropometric trends in preterm infants born before 28 weeks' gestation underscore the increase in disproportionate growth over the years. Average weight and length *z* scores at NICU discharge were compared from 1997 to 2012. Over the years, weight *z* scores have continued to improve but length *z* scores have remained substantially lower than weight *z* scores. As a result, since 2002, BMI *z* scores have been above the reference median. (53)

The difference in body composition between preterm infants at term-equivalent age and term-born infants is likely multifactorial. The Fig shows the potential mechanisms responsible for the difference in body composition including the body composition at birth as well as nutritional and non-nutritional factors that affect the postnatal accretion of lean tissue and fat. Currently, the body composition of preterm infants can be directly measured using techniques such as dual-energy x-ray absorptiometry, magnetic resonance imaging, or air displacement plethysmography. However, body composition is not routinely measured in the NICU. Anthropometric indexes of body proportionality are potentially useful clinical tools to identify disproportionate growth during the NICU hospitalization. (54) BMI curves for preterm infants have been developed to serve this purpose. (14)(55) A limitation of this approach is that body proportionality indexes such as BMI (weight divided by length squared) fail to identify growth alterations when both weight and length are affected in the same direction (both inadequate or excessive). In addition, in both preterm and term infants, BMI is a poor surrogate for directly estimated adiposity. (56)(57) Nonetheless, the assessment of body proportionality does provide additional clinical information about the growth status of preterm infants. (54) Clinicians tracking the proportionality of growth may be better equipped to identify disproportionate growth and adjust nutritional care accordingly.

CONCLUSIONS

Accurate assessment and careful monitoring of the postnatal growth of preterm infants is needed to achieve optimal long-term outcomes. None of the preterm growth curves available is without limitations. To date, the intrauterine growth references remain the most accepted and align with the AAP recommended growth target: the healthy reference fetus. A preterm postnatal growth standard that uses the healthy preterm infant as the reference is now available but is limited by the small number of very preterm infants used to construct the curves for lower gestational ages. How useful a growth curve might prove to be in clinical practice will depend on the questions being addressed. Clinicians should understand how growth curves were created, the underlying reference population, their intended use, and their strengths and limitations. *Z* score change over time is preferable to cross-sectional assessments of size and better predicts long-term outcomes. Preterm infants at term-equivalent age have a different body composition than term-born infants, with less lean tissue and more adipose tissue. Tracking body proportionality indexes using BMI curves can potentially help clinicians make more informed nutritional interventions with the potential to optimize long-term health.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the maternal, placental, and fetal factors that affect intrauterine fetal growth.
- Know how body composition changes during postnatal growth and development and understand the effect of prematurity.
- Know the postnatal growth patterns of SGA infants.
- Know the definitions, causes, clinical features, differential diagnosis, and typical laboratory findings of SGA and LGA infants.
- Know the importance of prenatal and postnatal nutrition on neurodevelopmental outcomes, including the importance of breast milk for brain development.

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Intravenous Lipid Emulsions in the NICU

Kara L. Calkins, MD, MS,* Daniel T. Robinson, MD, MSc†

*Department of Pediatrics, Division of Neonatology & Developmental Biology, Neonatal Research Center of the UCLA Children's Discovery and Innovation Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA

†Department of Pediatrics, Northwestern University Feinberg School of Medicine and Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

Education Gaps

Intravenous lipid emulsions provide a concentrated source of calories and fatty acids. Traditional lipid emulsions are composed of soybean oil. New lipid emulsions rely on other oil sources (olive, coconut, and fish oil). As a result, the safety and nutritional profile is altered. Neonatologists should understand the composition of various lipid emulsions and how they affect clinical outcomes.

Abstract

The clinical goals of intravenous lipid emulsions (ILEs) have changed since their initial development. In the past, 100% soybean oil was used to provide energy and prevent an essential fatty acid deficiency. Now, different oil sources are used with the goal of improving nutritional status and preventing common neonatal comorbidities. We now have a better understanding of specific ILE constituents, namely, fatty acids, vitamin E, and phytosterols, and how these components contribute to complications such as intestinal failure–associated liver disease. This review addresses the development and composition of different ILEs and summarizes how individual ILE ingredients affect infant metabolism and health.

Objectives After completing this article, readers should be able to:

1. Summarize the historical changes in oils tested and used during the development of intravenous lipid emulsions.
2. Identify key differences in fatty acid composition amongst intravenous lipid emulsions.
3. Describe the suggested mechanisms by which inflammation, oxidative stress, and phytosterols impair liver function and contribute to intestinal failure–associated liver disease.

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ABBREVIATIONS

ALA	α-linolenic acid
ARA	arachidonic acid
DHA	docosahexaenoic acid
EFAD	essential fatty acid deficiency
EPA	eicosapentaenoic acid
FDA	Food and Drug Administration
FXR	farnesoid X receptor
IFALD	intestinal failure–associated liver disease
ILE	intravenous lipid emulsion
LA	linoleic acid
LXR	liver X receptor
MCT	medium-chain triglyceride
PN	parenteral nutrition
PUFA	polyunsaturated fatty acid
SO	soybean oil

INTRODUCTION

Parenteral nutrition (PN) has improved survival rates and reduced comorbidities for premature infants and infants with intestinal failure. During prolonged periods of fasting or limited enteral nutrition, PN ensures that neonates receive fluids, electrolytes, carbohydrates, protein, and micronutrients. Intravenous lipid emulsions (ILEs) complement PN and are a source of nonprotein calories and fatty acids. For several decades, the mainstay ILE has been derived from soybean oil (SO). Soybeans have an exceptionally high content of linoleic acid (LA), an omega (ω)-6 fatty acid. High ω-6 to ω-3 ratios, combined with a lack of antioxidant protection, excite inflammation and oxidative stress. SO is also rich in phytosterols, plant-derived compounds that reduce biliary flow and contribute to intestinal failure–associated liver disease (IFALD). (1)(2)(3)(4)(5)(6)

To limit toxicities associated with SO, new ILE generations have emerged. By replacing SO with olive, coconut, and fish oil, an ILE's biological properties are modified—the fatty acid profile is diversified, the phytosterol concentration is decreased, and the antioxidant capacity is increased (Table). These compositional changes alter the ILE's ability to modulate inflammation, oxidation, and disease. In this review, we will examine the history of ILEs, types of ILEs, and how intravenous fatty acids, phytosterols, and antioxidants affect clinical outcomes, specifically IFALD.

WHY ARE ILEs IMPORTANT?

PN should provide an appropriate amount of carbohydrates, protein, and fat to ensure optimal growth and development. Before the advent of ILEs, high-dextrose, fat-free PN was prescribed. As a result, patients developed hyperglycemia, essential fatty acid deficiencies (EFADs), fatty liver, and hyperinsulinemia, causing hypoglycemia. The goal of an ILE is to provide a dietary fuel in the form of fatty acids and prevent an EFAD. Fatty acids are hydrocarbons with a methyl end and carboxyl group end. Fatty acids exist in 3 forms, triglycerides, phospholipids, and cholesterol esters, and are characterized by their length (short, medium, long, or very long), desaturation (whether the carbon chain contains double bonds), double bond number (mono- or polyunsaturated), double bond location (ω-3, ω-6, or ω-9), and double bond orientation (Fig 1). In addition to providing energy, fatty acids have several critical roles—they regulate cell membrane structure, cellular pathways and signaling, transcription factor activity, and gene expression. Moreover, the polyunsaturated fatty acids (PUFAs) docosahexaenoic acid (DHA) and arachidonic acid (ARA) are vital for growth and brain development and serve as precursors to eicosanoids, cell-signaling molecules that regulate inflammation, immunity, and vasoreactivity. (7)(8)(9) While the ω-6 fatty eicosanoids are proinflammatory, the ω-3 eicosanoids are less inflammatory (Fig 2).

There are 3 PUFA types—ω-6, ω-3, and ω-9 (Fig 1). LA and α-linolenic acid (ω-3, ALA) are referred to as "essential fatty acids." In contrast to plants, humans lack the enzymes to place a double bond at the n-6 and n-3 position. Consequently, LA and ALA must be consumed in the diet. An EFAD can be reversed with ω-6 fatty acids alone, including ARA. As a result, many have questioned the "essentiality" of LA and ALA. (8)(10) Oleic acid, an ω-9 fatty acid, is the only fatty acid that can be synthesized de novo in mammals. The parent fatty acids LA, ALA, and oleic acid give rise to very-long-chain PUFAs via elongation and desaturation. LA is broken down to ARA; ALA is metabolized to eicosapentaenoic acid (EPA) and DHA; oleic acid is metabolized to Mead acid (Fig 2). However, the production rates for these downstream moieties differ. First, fatty acid substrates compete for the same enzymes. Second, enzymes demonstrate "preferences" (ω-3 > ω-6 > ω-9). Third, conversion rates differ. In contrast to ARA synthesis, DHA synthesis is inefficient. Less than 5% of ALA is converted to DHA. (11) Hence, an exogenous source may be required to maintain adequate DHA levels.

The triene-to-tetraene ratio (Mead acid to ARA) is used to define an EFAD biochemically. (12)(13)(14) When LA and ALA concentrations are low, there is a compensatory increase in Mead acid production. Traditionally, a triene-to-tetraene ratio greater than 0.2 is considered diagnostic of an EFAD. (12) Fatty acid status is influenced by age, gestational age, sex, dietary intake, and ILE type. Single nucleotide polymorphisms of desaturase enzymes (FADS1/FADS1) also influence PUFA status. More contemporary technology better quantifies fatty acids, specifically Mead acid. Consequently, diagnostic ranges that are lower than the 0.2 threshold have been cited for infants and children. (13) Biochemical EFADs generally precede clinical manifestations and do not account for an individual's ω-3 status. A classic sign of an EFAD includes a scaly skin rash. This occurs because LA is an important component of ceramides, lipids that help preserve skin integrity. Other signs and symptoms include thrombocytopenia, platelet dysfunction, poor wound healing and growth, increased infection susceptibility, elevated liver enzymes, and hyperlipidemia.

At least 1% of calories should be derived from LA to prevent an EFAD. Ideally, 3% to 4% of calories should be derived from LA, and 0.25% to 0.5% should be derived from

TABLE. **Intravenous Lipid Emulsions**

	1st GENERATION	2nd GENERATION	3rd GENERATION	4th GENERATION	
	INTRALIPID[a]	**LIPOFUNDIN**[b]	**CLINOLEIC**[c]	**SMOF**[d]	**OMEGAVEN**[d]
Oil source (%)					
Soybean oil	100%	50%	20%	30%	0%
Coconut oil	0%	50%	0%	30%	0%
Olive oil	0%	0%	80%	25%	0%
Fish oil	0%	0%	0%	15%	100%
Egg phospholipid (10 g/100 ml)	1.2	12	1.2	1.2	1.2
Fatty acid (% by weight)					
Medium chain					
Caprylic	0%	27.0%	0%	16.0%–20.5%	0%
Capric	0%	17.95%	0%	9.85%–13.0%	0%
Long chain					
Linoleic acid (18:2n-6)	54.68%	28.89%	18.56%	17.5%	1.5%
α-Linolenic acid (18:3n-3)	6.65%	0%	1.71%	2.25%	1.1%
Arachidonic acid (20:4n-6)	0%	0.19%	0.16%	0.5%	0.2%–2.0%
Docosahexaenoic acid (22:6n-3)	0%	0.06%	0%	1.0%–3.5%	14.0%–27.05%
Eicosapentaenoic acid (20:5n-3)	0%	0%	0%	1.0%–3.5%	13.0%–26.0%
Oleic acid (18:1n-9)	20.92%	11.68%	59.69%	23.0%–35.0%	4.0%–11.0%
ω-6 to ω-3 Ratio	7:1	7:1	9:1	2.5:1	1:8
Phytosterols (mg/L)					
B-sitosterol	302.6	191.6	240.6	131.6	0
Campestrol	55.4	30.9	13.3	20.5	1.0

Continued

TABLE. (Continued)

	1st GENERATION	2nd GENERATION	3rd GENERATION	4th GENERATION	
	INTRALIPID[a]	LIPOFUNDIN[b]	CLINOLEIC[c]	SMOF[d]	OMEGAVEN[d]
Stigmasterol	65.1	46.0	12.2	18.5	1.4
Vitamin E (μg/mL)					
α-tocopherol		132.0	32.0	164.5	230.0
FDA approval					
	Approved in the United States for children and adults	Not approved in the United States	Approved in the United States for adults	Approved in the United States for adults	Approved in the United States for children for the management of IFALD

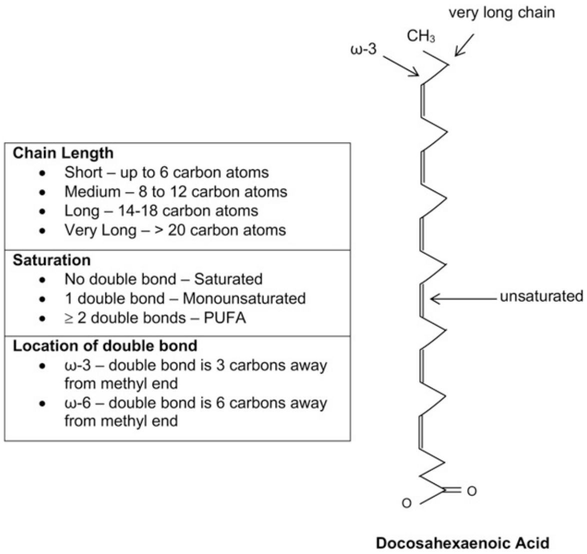
FDA=Food and Drug Administration; IFALD=intestinal failure-associated liver disease.

[a] *Fresenius Kabi, Uppsala, Sweden.*

[b] *B-Braun, Melsungen, Germany.*

[c] *Baxter, Deerfield, IL.*

[d] *Fresenius Kabi, Bad Homburg, Germany.*



Chain Length
- Short – up to 6 carbon atoms
- Medium – 8 to 12 carbon atoms
- Long – 14-18 carbon atoms
- Very Long – > 20 carbon atoms

Saturation
- No double bond – Saturated
- 1 double bond – Monounsaturated
- ≥ 2 double bonds – PUFA

Location of double bond
- ω-3 – double bond is 3 carbons away from methyl end
- ω-6 – double bond is 6 carbons away from methyl end

Figure 1. Fatty acid nomenclature. PUFA=polyunsaturated fatty acid.

ALA. The current recommended dietary intake for LA for preterm and term infants is 0.25 g/kg per day and 0.1 g/kg per day, respectively. (15) Because fatty acid stores are limited in infants, particularly preterm infants, biochemical EFADs can manifest within 2 to 3 days of initiating fat-free PN. (16) Because each ILE has a different fatty acid composition, the dose to prevent an EFAD varies among ILEs. At a minimum, 0.5 g/kg per day of SO is required to prevent an EFAD. However, other ILEs require a higher dose. (14)(16) In addition, because some oils lack LA, ALA, and ARA entirely (eg, coconut oil) or contain a relatively small amount of LA and ALA (eg, olive oil), they are combined with SO to prevent an EFAD.

HISTORY OF ILEs

The history of ILEs dates back to the 1700s when dogs were infused with olive oil. These animals developed respiratory distress and died, most likely secondary to a fat embolism. In the 1800s, subcutaneous milk injections were administered to a malnourished adult with tuberculosis. Later, milk was infused into patients with cholera. (17) In the 1920s and 1930s, Japanese and American scientists began to explore how to best manufacture an oil-in-water solution. By this time, it was recognized that hydrophobic lipids would need to be dispersed in a solution for safe intravenous infusion. To accomplish this, emulsifiers such as egg yolks were added. By coating the lipid droplets, egg phospholipids ensure that lipid droplets remain soluble in an aqueous phase. Finally, in the 1960s, the first commercially available ILE (Lipomul®, Upjohn Company, Kalamazoo, MI) was introduced. However, this cottonseed-derived ILE was later removed from the market because of adverse reactions. (17)

In the 1960s, the first stable ILE was developed. A Swedish scientist combined SO with an egg phospholipid emulsifier (Intralipid®, Fresenius Kabi, Uppsala, Sweden). This 100% SO-based ILE is now deemed a first-generation ILE (Table). Vegetable oils such as SO contain fatty acids, mainly in the form of long-chain triglycerides containing PUFAs. Over the past couple of decades, many people have criticized SO's ratio of proinflammatory ω-6 to ω-3 (7:1), long-chain triglyceride and phytosterol content, and poor supply of antioxidants, DHA and ARA. (2)(4)(18)(19)(20)(21) In 1984, a second-generation ILE (Lipofundin®, B-Braun, Melsungen, Germany) combined medium-chain triglycerides (MCTs) with SO in equal proportions (50:50) (Table). Compared with long-chain triglycerides in SO, MCTs offer several advantages. MCTs are derived from tropical nut oils (coconut oil) and are saturated fatty acids with a carbon length of 6 to 10. MCTs are quickly hydrolyzed in the small intestine and directly transported to the liver for metabolism. In contrast, long-chain triglycerides are re-esterified in the intestine and incorporated in chylomicrons, which are transported to the lymphatic system and oxidized or stored in adipose or hepatic tissue. Hence, MCTs are rapidly metabolized. Moreover, in contrast to PUFAs, MCTs are not converted into eicosanoids and are immune neutral.

In the 1990s and beyond, olive and fish oil were introduced. A third-generation ILE (ClinOleic®, Baxter, Deerfield, IL) combined 80% SO with 20% olive oil (Table). Olive oil is enriched with the antioxidant vitamin E, and its main primary fat is oleic acid, a ω-9 monounsaturated fatty acid. PUFAs are highly susceptible to oxidative reactions, which produce a cascade of peroxides and free radicals that cause cell damage. In contrast, saturated and monounsaturated fatty acids are more resistant to oxidant stress. Because monounsaturated fatty acids replace PUFAs, olive oil–based ILEs are thought to reduce lipid peroxidation and inflammation.

The latest and fourth-generation ILEs are enriched with fish oil and vitamin E (SMOF®, Fresenius Kabi, Bad Homburg, Germany, and Omegaven®, Fresenius Kabi, Bad Homburg, Germany) (Table). Fish oil supplies DHA and EPA, 2 PUFAs not present in SO, and MCT- and olive oil–based ILEs. As a result, fish oil is considered to be anti-inflammatory. SMOF is a fish oil–based composite lipid emulsion, which contains a mix of SO, MCTs, olive oil, and fish oil and has ω-6 to ω-3 ratio of 2.5:1. SMOF is approved by the US Food and Drug Administration (FDA) for use in adults only and, hence, is used off-label in pediatrics. Omegaven is composed of 100% fish oil and is FDA approved as monotherapy for pediatric IFALD.

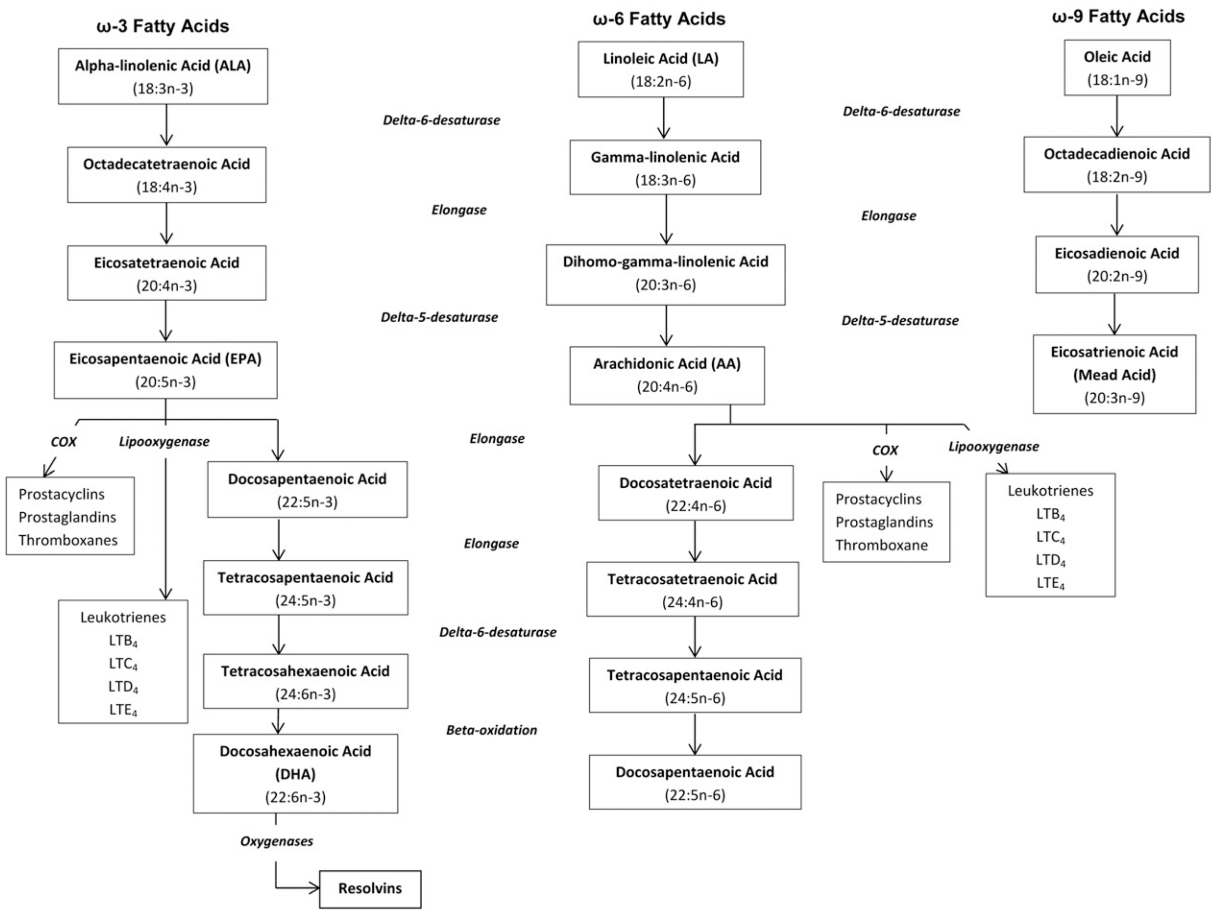


Figure 2. Polyunsaturated fatty acid metabolism.

(5)(18)(19)(20)(21)(22) Because of the high PUFA content in fourth-generation ILEs, vitamin E is added to counteract lipid peroxidation. Vitamin E has 8 isoforms (α, β, γ, and δ tocopherol and α, β, γ, and δ tocotrienol). SO contains a small amount of γ-tocopherol, whereas the fish oil–based ILEs contain a higher amount of α-tocopherol, the most biologically active vitamin E isoform (Table).

PUFAs AND ILEs

Preterm neonates are not only at risk for EFADs, but also exhibit declining DHA and ARA levels soon after birth. (23)(24) This occurs for several reasons. First, preterm infants are born before placental biomagnification. Biomagnification describes the phenomenon of preferential transfer of ARA and DHA over LA and ALA, which lead to higher ARA and DHA umbilical cord concentrations compared with maternal serum concentrations. ARA and DHA whole-body fetal accretion accelerates in the third trimester of pregnancy and is estimated to be approximately 212 mg/kg per day and 45 mg/kg per day, respectively. (25) Second, after delivery, although term infants receive human milk or formula enriched with ARA and DHA, most preterm infants initially receive limited enteral nutrition. Third, preterm infants' conversion rates of LA and ALA into the downstream PUFAs are insufficient to meet estimated requirements. (25) As a result, preterm infants fail to meet fetal accretion rates and quickly demonstrate an ARA and DHA deficiency. (23)(24)

ARA and DHA are essential for central nervous system development and support the developing visual system by regulating retinal angiogenesis and vascularization. ARA and DHA rapidly accumulate in the brain not only during fetal life, but also during the first 2 years of age. ARA and DHA are important for neuronal and cell signaling, cell trafficking, myelination, long-term potentiation, growth and repair, and hippocampal development. Studies in animals and infants have demonstrated that diets lacking ARA and DHA are associated with poor cognition, attention, and behavioral outcomes compared with diets supplemented with DHA and ARA. (7)(8) Research has highlighted that

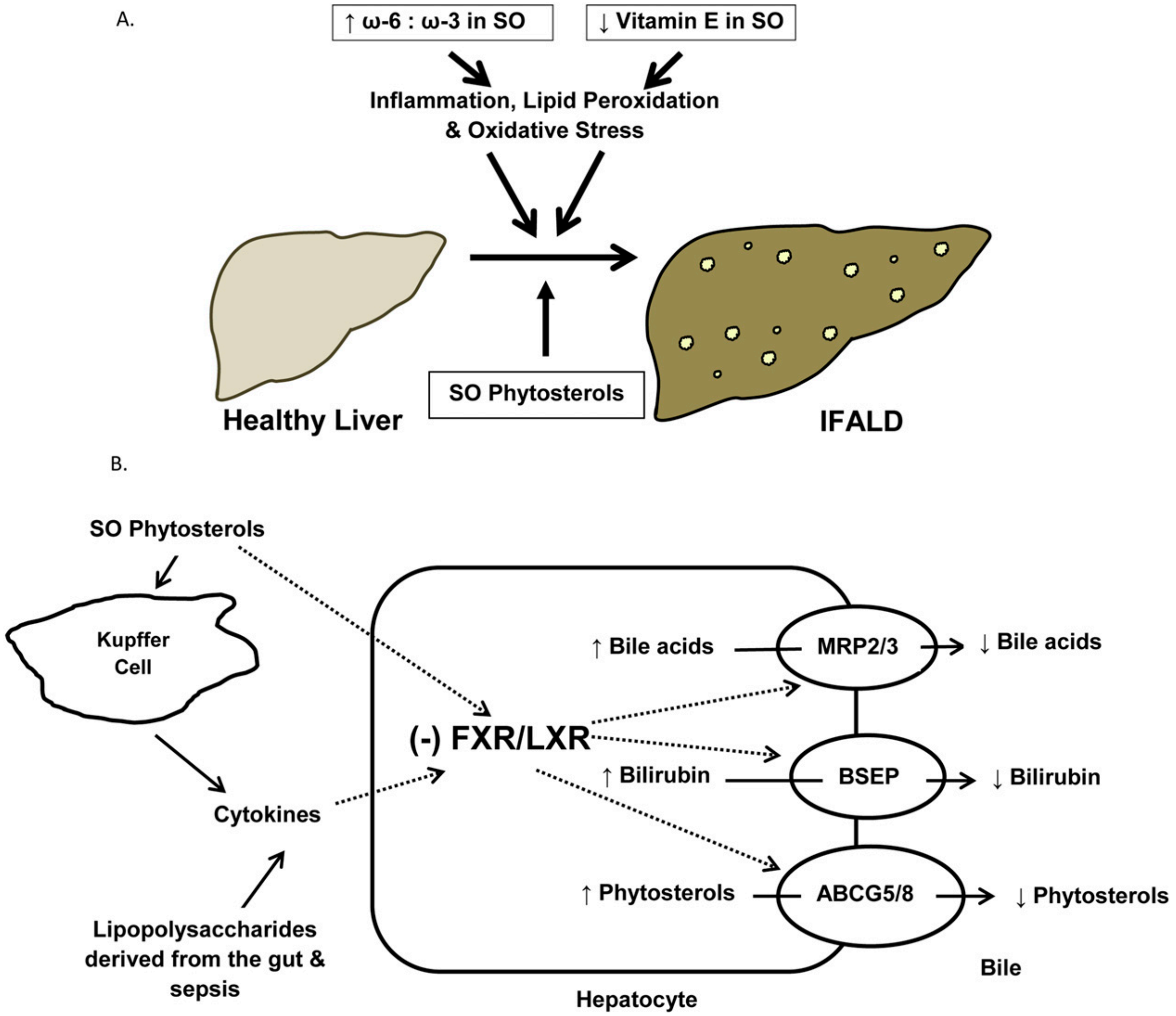


Figure 3. A. Intravenous SO and IFALD. B. SO and bile acid metabolism. ABCG5/8=ATP-binding cassette transporters; BSEP=bile sale export pump; FXR=farnesoid X receptor; IFALD=intestinal failure–associated liver disease; LXR=liver X receptor; MRP=multidrug resistant protein; SO=soybean oil.

the "optimal" ratio of ARA to DHA in formula is approximately 2:1 and that high levels of DHA decrease ARA. (7)(9)(26) Human milk contains more ARA than DHA, and concentrations of ARA are generally stable, whereas DHA concentrations vary depending on a mother's diet and genetics. (27)

To mitigate the DHA deficiency observed with traditional ILEs, a fish oil–based composite ILE is sometimes used. At a dose of 2.5 mg/kg per day or higher, this ILE matches in utero accretion rates. As expected, preterm infants who receive a fish oil–based composite ILE demonstrate improved DHA status. However, these infants still exhibit a decline in DHA and ARA. (23)(24)(28) Other studies have reported lower ARA levels in preterm infants who receive a fish oil–based composite ILE compared with preterm infants who receive SO. (23) Despite providing some ARA, the high EPA content in a fish oil–based composite ILE and 100% fish oil may inhibit the conversion of LA to ARA.

In a single-site study in the Netherlands, 96 infants with a mean gestational age of 27 weeks were randomized to 1 of 5 arms. (24) Control subjects received a standard dose of amino acids (2.4 g/kg per day) at birth and SO on the second day after birth (1.4 g/kg per day). Two interventional groups received the standard dose of amino acids and a high dose of ILE (2 g/kg per day of SO or a fish oil–based composite ILE) shortly after birth. The other 2 interventional groups received high-dose amino acids (3.6 g/kg per day) and ILEs, either SO or a fish oil–based composite ILE. Compared with the SO group, the group that received the fish oil–based composite ILE demonstrated a more positive and larger change in weight and head circumference *z* scores at hospital discharge that was statistically significant.

(24) Moreover, at 2 years of age, the group that received high-dose amino acids and a high dose of the fish oil–based composite ILE had a greater body weight than the other groups. (29) Although other studies failed to replicate any short-term growth benefit, some have demonstrated a decreased incidence of retinopathy of prematurity with a fish oil–based composite ILE and slower rise in conjugated bilirubin in infants and children with intestinal failure. (30)(31)(32) Further research is required to confirm the impact of fish oil ILEs on long-term growth and cognition.

PHYTOSTEROLS AND ILEs

Phytosterols, sitosterol stigmasterol, and campesterol, unlike cholesterol, a similarly structured sterol, are not endogenously synthesized. These sterol molecules contain 2 common elements, a nucleus and side chain. The mammalian sterol cholesterol and plant-based phytosterols' nucleus contain the same 4-ring structure. However, the side chain differentiates these molecules from one another. (33) Under normal physiologic circumstances, the small intestine absorbs less than 5% of ingested phytosterols. The adenosine triphosphate–binding cassette transporters (*ABCG5/8*) excrete sterols from the enterocyte back into the intestinal lumen for fecal elimination. The small amount of phytosterols that enter the systemic circulation are excreted by the hepatic transporter *ABCG5/8* (Fig 3). Because phytosterol intestinal absorption is low and hepatic excretion is high, circulating phytosterol concentrations are minimal.

Sterols intercalate in the phospholipid bilayer of cell membranes. An increased concentration of phytosterols in the membrane reduces the amount of cholesterol and decreases membrane fluidity. Cell membrane alteration also occurs when ω-3 fatty acids are displaced by ω-6 fatty acids. A decrease in membrane fluidity impairs the function of membrane-bound receptors and enzymes. In red blood cell membranes, increased membrane fragility causes cell lysis and the release of bilirubin.

The phytosterol concentration is highest in 100% SO and negligible in 100% fish oil (Table). Because ILEs bypass the enterocyte's mechanism of phytosterol removal, phytosterol blood levels rapidly increase. Plasma levels of total phytosterols directly correlate with the cumulative phytosterol intake. (34) Kinetics of plasma sterol levels measured in preterm infants exposed to SO suggest that a steady state is achieved 3 to 5 days after infusion initiation. (35) Infants with lower gestational ages may have higher steady-state levels compared with more mature infants. The phytosterol half-life appears to be longer in preterm infants with IFALD than in preterm infants without hepatic dysfunction. (36) Although phytosterol levels decrease after ILE discontinuation, this may take longer than 2 weeks, particularly in cholestatic preterm infants. (35)

Phytosterols contribute to IFALD by disrupting bile acid homeostasis in 2 specific ways. First, phytosterols block cholesterol 7-α-hydroxylase, which is the rate-limiting step in the conversion of cholesterol to bile acids. Second, phytosterols, specifically stigmasterol, inhibit farnesoid and liver X receptor (FXR and LXR) signaling. (1)(2) FXR and LXR are 2 nuclear receptors that orchestrate the uptake and removal of bile acids, bilirubin, and sterols via the regulation of several transporters (bile salt export pump encoded by *ABC11*, multidrug resistant protein 2 encoded by *Abcc2,* and sterolin 1/2 encoded by *ABCG/8*) (Fig 3). In mice, adding stigmasterol to 100% fish oil impaired bile secretion by downregulating FXR-dependent genes and simultaneously activating hepatic macrophages (Kupffer cells). (2) As a result, these mice developed cholestasis and elevated liver enzymes and function tests. In contrast, mice that received 100% fish oil were free of liver disease. (2) In children with intestinal failure, stigmasterol correlates with conjugated bilirubin and histologic changes on liver biopsy. (3) In piglet models, adding phytosterols to 100% fish oil did not induce liver injury, and vitamin E appeared to be a key protective agent. (4) However, with in vitro testing of porcine cells, phytosterols exacerbated the Kupffer cells' inflammatory response triggered by lipopolysaccharides. (6) These experiments suggest that inflammation and intravenous phytosterols act synergistically to cause IFALD (Fig 3). (2)

INTESTINAL FAILURE AND ILEs

Intestinal failure is defined as a "reduction of gut function below the minimum necessary for the absorption of macronutrients, water, and electrolytes such that intravenous nutrition is required to maintain health and/or growth." (37) The most common cause of intestinal failure in children is short bowel syndrome, an acquired or congenital disorder characterized by a reduction in intestinal surface area. In premature infants, necrotizing enterocolitis is the leading cause of short bowel syndrome and intestinal failure. In term infants, common causes include midgut volvulus, intestinal atresias, and abdominal wall defects. (38) One of the most common complications associated with prolonged PN is IFALD, a multifactorial disease hallmarked by conjugated hyperbilirubinemia (>2 mg/dL [34.2 μmol/L]) in the absence of other liver diseases. On liver biopsy, cholestasis and periportal inflammation are characteristic of IFALD. IFALD can quickly progress, particularly in preterm infants, to liver fibrosis and cirrhosis. (39) PN duration, gestational age, birthweight, intestinal anatomy, lack of enteral nutrition and enterohepatic circulation, bacterial gut translocation, and sepsis are well-established risk factors for IFALD. Moreover, PN composition, specifically ILE dose and type, have been associated with IFALD. (2)(4)(18)(19)(20)(21)(40)(41)(42)

Before the advent of fourth-generation ILEs, children with intestinal failure were subjected to fat-free PN and SO dose reduction to prevent and treat end-stage liver disease. Although low-dose SO is associated with a slower rise in conjugated bilirubin, doses of less than or equal to 1 g/kg per day are associated with growth failure and EFADs, particularly in preterm infants. (40)(41)(42) In 2018, the Food and Drug Administration approved fish oil monotherapy for the management of pediatric IFALD. In the United States, before 2018, fish oil monotherapy dosed at 1 g/kg per day was prescribed under compassionate use protocols as a salvage therapy for IFALD. Most studies investigating fish oil monotherapy for IFALD treatment are single-site studies that use historical controls. (19)(20)(21)(43)(44) To date, only 1 randomized controlled trial has been conducted to investigate the efficacy of fish oil monotherapy. Lam et al randomized infants with IFALD and a median gestational age of 29 weeks to either 1.5 g/kg per day of SO or fish oil monotherapy. (18) During the study, there was an increased awareness of the benefits of fish oil monotherapy. As a result, parents were unwilling to randomize their child to the SO group, and the study was halted after enrolling only 16 subjects. Although there was no statistical difference in the study's primary outcome (ie, the number of cases with IFALD resolution), other results were noteworthy. Compared with SO, the fish oil monotherapy group had a significantly slower rise in conjugated bilirubin. Moreover, despite receiving a similar amount of calories from ILE and enteral nutrition, patients who received the fish oil monotherapy demonstrated better growth. (18)

When combined with a contemporary, multidisciplinary approach to intestinal failure, fish oil–based ILEs are associated with a reduction in liver dysfunction and end-stage liver disease requiring transplantation. (19)(20)(21)(43)(44) In general, biochemical IFALD resolution occurs in approximately 75% of children with IFALD after approximately 8 to 12 weeks of rescue treatment with fish oil monotherapy. (19)(20)(43)(44) Response rates are correlated with the severity of liver disease, gestational age, birthweight, and other comorbidities. (21)(22) Despite a low supply of LA and ALA, infants and young children who receive fish oil monotherapy demonstrate normal triene-to-tetraene ratios and Mead acid concentrations. (45) DHA and EPA levels increase substantially and ARA levels decline with fish oil monotherapy. (45) However, despite a decrease in ARA and ILE dose of 1 g/kg per day, most infants do not exhibit growth failure. (21)(43)(44) Increased dextrose provisions, cholestasis resolution, and improved tolerance and absorption of enteral nutrition most likely contribute to this growth pattern.

When comparing fish oil monotherapy to fish oil–based composite ILEs, composite ILEs are dosed at more than 1 g/kg per day and, hence, provide more fat calories. However, fish oil–based composite ILEs still expose the liver to phytosterols. In a meta-analysis of 3 studies with 93 subjects, fish oil–containing ILEs were 6 times more likely to reverse IFALD. Two of the 3 studies compared SO to fish oil monotherapy, whereas 1 study compared SO to a combination of SO, olive oil, and fish oil. (46) Studies are somewhat conflicting about IFALD prevention. In preterm infants who require a short course of PN, fish oil–based composite ILEs do not appear to offer a significant hepatoprotective benefit. However, in young infants and children with intestinal failure, fish oil–based composite ILEs may decrease the incidence and severity of IFALD. (32)(46)(47) There has yet to be a study comparing fish oil monotherapy to a fish oil–based composite ILE for the treatment of IFALD.

CONCLUSION

Over the past several decades, the number of ILE types has increased and our understanding of ILEs has changed. The newer generation of ILEs contains less long-chain triglycerides and phytosterols and more DHA and vitamin E. Ideally, a "fifth" generation of ILEs will be developed for the growing preterm neonate and young infant and child. These new ILEs will hopefully supply sufficient energy as fat to support somatic and brain growth, permit accrual of appropriate proportions of ARA and DHA, eliminate phytosterols, and provide sufficient antioxidant protection to prevent lipid peroxidation. The overall clinical goal of any ILE should be to safely enhance growth and development without causing organ injury, specifically IFALD.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical and laboratory features of essential fatty acid deficiency and how to prevent it.
- Distinguish between essential and nonessential fatty acids.
- Recognize the association of cholestasis with total parenteral nutrition, know how to manage this, and understand how to diagnose other possible causes.

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Index of Suspicion in the Nursery

1 Newborn Who Cannot Open Eyes

Babina Nayak, MD,* Cheng Zhang, MD,[†] Suhas Nafday, MD,*
Tomas Havranek, MD*

*Division of Neonatology, Department of Pediatrics, and [†]Department of Ophthalmology, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY

PRESENTATION

A female infant is born at 40 weeks 2 days gestational age to a 52-year-old gravida 8, para 7 mother via vaginal delivery with Apgar scores of 9 and 9. The infant is admitted to the NICU for mild respiratory failure that needed continuous positive airway pressure (CPAP) support and for further evaluation of neurologic malformation diagnosed on prenatal ultrasonography.

The maternal history is significant for advanced maternal age and consanguinity (first-degree cousins). The infant's physical examination findings are significant for decreased range of motion and increased tone in all 4 extremities.

In the NICU, the infant is noted to have recurrent apnea associated with abnormal rhythmic movements concerning for neonatal seizures. However, 24-hour continuous video electroencephalography (vEEG) does not demonstrate electrographic seizures and there is no correlation between cortical wave function and her inability to open eyes. Although she blinks rapidly in response to light and brisk pupillary stimulus, she does not spontaneously open her eyes on either side, for which she is evaluated by ophthalmology. There are no signs suggestive of Horner syndrome. Fundus examination by the pediatric ophthalmologist reveals the presence of an optic nerve with a large, deep cup (0.5 in the right eye and 0.65 in the left eye), minimal temporal pallor in the left eye, and unremarkable retina and macula in both eyes with no disc edema or retinal hemorrhage.

Horner syndrome is ruled out. Genetic consultation finds a SNIP array with regions of heterozygosity, which would be expected given that the parents are first cousins; however, no microdeletions or duplications are found and the mother declines follow-up genetic testing.

Both admission and repeat laboratory parameters, including thyroid function tests and creatine phosphokinase obtained as advised by pediatric neurology, are unremarkable. Renal/bladder ultrasonography findings are normal, spinal ultrasonography shows low-lying conus at L2. Prenatal diagnosis of mild pulmonic stenosis and Dandy-Walker variant (DWV) are confirmed on postnatal imaging including echocardiography and magnetic resonance imaging (MRI) of the brain. MRI of the brain also shows absent corpus callosum, hypoplasia of the hippocampus, and hypoplastic cerebellar vermis, with mild dilation of lateral ventricles and enlargement of fourth ventricle with no associated hydrocephalus. MRI of the orbits is pertinent for small optic nerves bilaterally, no signal abnormality along the optic nerves, optic chiasma, and visualized optic tracts. Polysomnography study is significant for primary central apnea.

The infant is discharged 6 weeks after birth with the diagnosis of severe bilateral ptosis and DWV. Unlike the cases of congenital ptosis presented in the

AUTHOR DISCLOSURE Drs Nayak, Zhang, Nafday, and Havranek have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

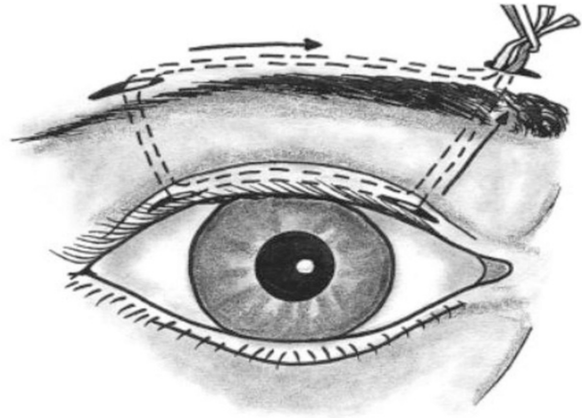

Figure. Frontalis sling (frontalis suspension) procedure primarily used for congenital ptosis. Most common surgery for congenital ptosis with poor levator muscle function. The upper eyelid is connected to the frontalis muscle with a sling.

literature, in our infant, both upper eyelids completely and symmetrically cover the sclera, giving her the normal appearance of a sleeping infant, leading to the initial diagnostic delay.

In the follow-up visits with ophthalmology, she eventually underwent bilateral frontalis sling surgery at 4.5 months of age (Fig).

After the corrective surgery she has gained some spontaneous eye movements more in the right eye than the left one and continues to follow up in the ophthalmology clinic for primary cortical visual impairment.

DISCUSSION

The Dandy-Walker complex is a spectrum of disorders affecting the development of the posterior fossa of the brain. It is characterized by inferior vermian hypoplasia and incomplete formation of the fourth ventricle, and has been associated with multiple congenital anomalies, radiographic abnormalities, and developmental delay. Although it may present with overlapping features, the usual mode of presentation includes seizures, apnea, hypotonia, spasticity in later life, and cerebellar signs such as ataxia and nystagmus, as well as irritability, vomiting, macrocephaly, and other features suggestive of hydrocephalus. Moderate to severe intellectual disability is a common finding but some cases have been reported to have normal intelligence with the condition (1)(2).

The DWV is on the lower end of the disease spectrum and is characterized by mild vermian hypoplasia and a normal-sized posterior fossa, with a small cystic cavity that communicates with the fourth ventricle. Isolated DWV is associated with good neurodevelopmental outcomes. DWV

TABLE. **Syndromes with Congenital Ptosis (8)**

Arima syndrome
Blepharophemosis, ptosis and epicanthus inversus syndrome
Cardiofaciocutaneous syndrome
Coach syndrome
Coffin-Siris syndrome
Congenital fibrosis of the extraocular muscles
Cornelia de Lange syndrome
Costello syndrome
Dandy-Walker syndrome
DiGeorge syndrome
Duane-radial ray syndrome
Dubowitz syndrome
Kabuki syndrome
Kearns-Sayre syndrome
Jacobsen syndrome
Leopard syndrome 1
Loeys-Dietz syndrome
McDonough syndrome
Miller-Diekerlissencephaly syndrome
Moebius syndrome
Muenke syndrome
Myasthenic syndrome
Neurofibromatosis type 1
Noonan syndrome
Pallister-Hall syndrome
Peter-Plus syndrome
Pierson syndrome
Potocki-Shaffer syndrome
Rubinstein-Taybi syndrome
Seathre-Chotzen syndrome
Shprintzen-Goldberg craniosynostosis
Smith-Lemli-Opitz syndrome
Smith-Magenis syndrome
Stiff person syndrome
Waardenburg syndrome
Warburg syndrome
Wolf-Hirschhorn syndrome

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is unlikely to be associated with other congenital anomalies, however, there are case reports of an association of DWV with hydrocephalus, abnormal radiographic findings, poor developmental outcomes, or other congenital anomalies (3).

Congenital ptosis is defined as ptosis that is present at birth or within the first year after birth. In severe cases of ptosis, the drooping eyelid can cover part of or the entire pupil interfering with vision (4)(5) and thus requires early intervention.

A rare sporadic case of blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) with a mutation in the *FOXL2* gene has been described. (6)

In 1 case report, the patient was reported to have de novo interstitial deletion of 3q22.3-q25.2 encompassing *FOXL2, ATR, ZIC1*, and *ZIC4*, with BPES syndrome, Dandy-Walker malformation, and global developmental delay (7). About 75% of congenital ptosis cases are unilateral (8). Other genetic forms of congenital ptosis include BPES and blepharophimosis-ptosis-intellectual disability syndrome linked to 3q22.3 and 12q23 gene locations, respectively (9). A group of systemic syndromes that commonly present with congenital ptosis is listed in the Table.

CONCLUSION

There are many known genetic forms of congenital ptosis associated with syndromes. About 75% of these are cases of unilateral congenital ptosis. Congenital ptosis is also known to be associated with Dandy-Walker syndrome, but no cases have been reported demonstrating an association of bilateral severe congenital ptosis with DWV.

This is a unique case of a newborn with prenatal diagnosis of DWV not associated with any genetic cause, presenting with no spontaneous eye opening bilaterally and later diagnosed to be a severe variety of bilateral congenital ptosis needing surgical correction.

Lessons for the Clinician

- Congenital ptosis is a clinical diagnosis and the management depends both on the degree of severity as well as its association with specific syndromes.
- Severe bilateral congenital ptosis can be associated with DWV and requires a multidisciplinary approach.
- All newborns diagnosed with DWV should undergo a thorough physical examination for motor eye movements, and if findings are abnormal, should be referred to ophthalmology for detailed eye examination.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the syndromes associated with abnormalities of the eye including cranio-facial abnormalities, coloboma, abnormalities of the orbit, the eyebrows, the eyelids, the eyelashes, the cornea, the iris, and the retina.

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2 Conjugated Hyperbilirubinemia in a Late Preterm Neonate

Nicole Flores-Fenlon, MD,* Smeeta Sardesai, MD, MS Ed†

*USC/LAC+USC Neonatal-Perinatal Medicine Fellowship Program, Division of Neonatology, Department of Pediatrics, LAC+USC Medical Center & Children's Hospital Los Angeles, Keck School of Medicine of USC, Los Angeles, CA

†Division of Neonatology, Department of Pediatrics, LAC+USC Medical Center & Children's Hospital Los Angeles, Keck School of Medicine of USC, Los Angeles, CA

PRESENTATION

A 1,770-g male neonate is born at 35 weeks and 2 days of gestation to a 31-year-old gravida 1, para 0 woman who was found to have prolonged premature rupture of membranes (PPROM), with an amniotic fluid index (AFI) of 2.4. Ultrasonography performed 1 month prior showed a normal AFI of 12.6 and a fetus with multiple anomalies: small chest, hyperechogenic bowel, bilateral clubbed feet, and intrauterine growth restriction. Prenatal maternal laboratory screening was unremarkable, except for a high rubella titer. The mother reports having a flulike syndrome during her pregnancy but does not recollect the presence of a rash. Group B *Streptococcus* (GBS) status is unknown.

The infant is born via spontaneous vaginal delivery. Apgar scores are 2 and 8 at 1 and 5 minutes, respectively. At birth, the infant is vigorous and cries immediately; however, his respiratory effort decreases, and he becomes limp, apneic, and cyanotic. Positive pressure ventilation is administered in the delivery room followed by continuous positive airway pressure (CPAP) for respiratory distress upon admission to the community hospital NICU.

The infant is weaned from CPAP and is breathing room air by 2 weeks after birth. An umbilical venous catheter is placed, a blood culture specimen is obtained, and treatment with ampicillin and gentamicin is initiated for PPROM and unknown GBS status. Physical examination findings are significant for a small-appearing infant (birthweight <10th percentile, length <10th percentile, head circumference 10th percentile), bilateral undescended testes, and bilateral clubfeet.

Because of the growth restriction and other anomalies, a workup is initiated in the NICU. Cranial ultrasonography performed on the day of birth is normal for age. Echocardiography on day 2 after birth shows a small patent ductus arteriosus and small patent foramen ovale. Complete abdominal ultrasonography performed to follow up on the prenatal ultrasonography shows normal liver texture and size, no intrahepatic or extrahepatic biliary dilation and a normal gall bladder. Full-body radiography (Fig 1) shows vertebral anomalies of the 7th, 8th, and 9th vertebrae. A basic metabolic panel obtained 12 hours after birth is remarkable for low sodium, calcium, magnesium, and phosphorous at 133 mEq/L (133 mmol/L), 7.2 mg/dL (1.8 mmol/L), 1.47 mEq/L (0.73 mmol/L), and 3.8 mg/dL (1.23 mmol/L), respectively, with an elevated creatinine at 1.7 mg/dL (150 μmol/L). In addition, the total bilirubin is 5.7 mg/dL (97.5 μmol/L), with a conjugated component of 1.0 mg/dL

AUTHOR DISCLOSURE Drs Flores-Fenlon and Sardesai have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

(17.1 μmol/L) at 12 hours after birth. Laboratory studies and cultures are reassuring against infection. Serial measurements of the infant's conjugated bilirubin reveal a rising trend over the first week after birth to a maximum of 4.7 mg/dL (80.4 μmol/L). His hepatic transaminases are normal. His stools remain pigmented. He is started on ursodiol treatment.

A karyotype and chromosomal microarray are sent, and an ophthalmology consultation reveals posterior embryotoxon in both eyes. Despite fortified breast milk, he has poor weight gain and despite the ursodiol, the conjugated bilirubin continues to rise. Therefore, the neonate is transferred to a tertiary children's hospital for further evaluation and management.

DISCUSSION

Conjugated hyperbilirubinemia is caused by impairment of bile flow secondary to an intrahepatic condition, such as generalized hepatocellular injury, or extrahepatic disorder, such as obstruction. (1) It is a common presenting feature of hepatobiliary dysfunction and is never physiologic or normal. Typical clinical features in an infant with cholestasis include jaundice, pale or acholic stools, and dark urine, hepatomegaly, and poor weight gain. In addition, the infant may have a coagulopathy, splenomegaly, signs of sepsis, intracranial hemorrhage, or severe liver disease leading to hyperammonemia and encephalopathy. (2)

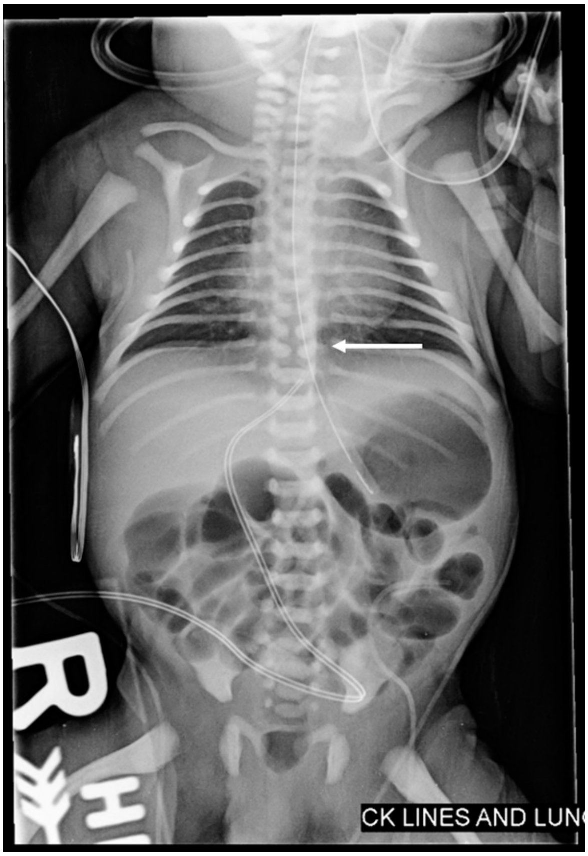

Figure 1. Full-body radiograph of the infant taken on the day of birth.

The differential diagnosis of cholestasis in an infant is broad and includes obstruction, infection, metabolic and endocrine abnormalities, and toxins. (3) Initial laboratory tests to perform, in addition to total and fractionated serum bilirubin, include a comprehensive metabolic panel, a complete blood cell count, coagulation studies, serologies for toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections, blood and urine cultures, serum bile acids, thyroid-stimulating hormone, thyroxine, α_1-antitrypsin concentration, and laboratory tests for metabolic disorders. (4) Imaging studies include abdominal ultrasonography and a cholescintigraphy (HIDA) scan to help distinguish obstructive from nonobstructive causes of cholestasis. Echocardiography and chest radiography should also be considered. In some cases, a liver biopsy may be required to make a definitive diagnosis, though some diseases are progressive, and the biopsy may not be diagnostic if it is performed early in the disease course. (5) Biliary atresia must be identified early and differentiated from other causes of neonatal cholestasis because surgical intervention before 2 months of age results in a better outcome.

For the infant described here, after he was transferred to the referral hospital, abdominal ultrasonography was repeated, which showed a nonvisualized gallbladder, and his stools were progressively more clay-colored in appearance. A HIDA scan did not visualize the gallbladder, and was suspicious for biliary atresia; therefore, a liver biopsy was considered (Fig 2). However, during this time, the results from microarray showed an approximately 14 Mb deletion of 20p13p12.1, which includes the *JAG1* gene. Haploinsufficiency of the *JAG1* gene is associated with Alagille syndrome. The remainder of his evaluation for inborn errors of metabolism was normal. He was eventually discharged from the hospital on oral feeds of a special commercial hypoallergenic infant formula and breastmilk fortified to 27 kcal/oz after demonstrating consistent weight gain for several days.

Alagille syndrome is a rare genetic disorder that can affect multiple organ systems and has a wide range of clinical phenotypes. It is an autosomal dominant disorder with variable penetrance that is caused most often by mutations in the *JAG1* (90% of patients) or *NOTCH2* gene. (6) It affects approximately 1 in 30,000 live births. It is

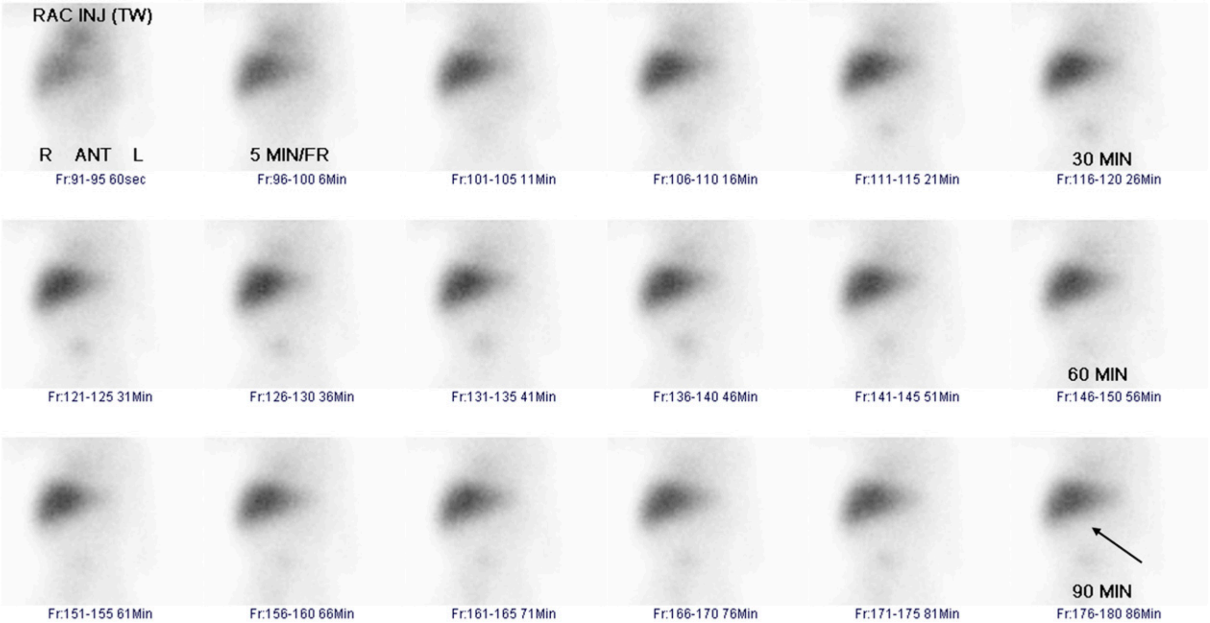

Figure 2. Cholescintigraphy scan showing nonvisualization of the gallbladder.

characterized by paucity of the interlobular bile ducts on histology, though the reduced number of bile ducts may not be apparent in infants younger than 6 months. It is commonly associated with chronic cholestasis, jaundice, cirrhosis, and pruritis. Cholestasis in the neonatal period is found in 95% of cases and may range in severity. Liver ultrasonography findings are often normal but may show a contracted gallbladder. Cardiac abnormalities such as peripheral pulmonic stenosis, tetralogy of Fallot, septal defects, and patent ductus arteriosus, are present in more than 90% of patients and is an important contributor to early survival. Butterfly vertebrae is typically associated with Alagille syndrome and is seen in 80% of cases, but other skeletal abnormalities include spina bifida occulta, vertebral fusion, and hemivertebrae and absence of the 12th ribs. Facial dysmorphisms include broad nasal bridge, triangular facies, deep-set eyes, and pointed chin. Intracranial vascular anomalies are found in up to 15% of patients on magnetic resonance angiography. These are often asymptomatic but can place the patient at risk for intracranial hemorrhage. (7) Additional findings include renal anomalies (intrinsic renal disease, cystic changes, renal tubular acidosis), short stature, and failure to thrive. (8)

The diagnosis of Alagille syndrome is made based on the characteristic clinical features and liver histology consistent with paucity of the bile ducts and confirmed with molecular DNA testing. (7) If there is clinical suspicion, genetic testing for the *JAG1* or *NOTCH2* mutation should be performed early in the evaluation to confirm the diagnosis, even in the absence of typical histologic findings. Laboratory findings in addition to conjugated hyperbilirubinemia and elevated hepatic transaminases can reveal extremely elevated γ-glutamyl transferase (up to 20 times the upper limit of normal). Echocardiography, renal ultrasonography, and ophthalmologic evaluation should be obtained in these infants as well.

Infants with Alagille syndrome are at high risk for growth failure secondary to impaired metabolism and absorption of fats. They often require fortified feeds, high daily caloric intake, and supplementation of fat-soluble vitamins. A nasogastric or gastrostomy tube may be necessary to achieve adequate nutrition. A hydrolyzed formula should be used because the medium-chain triglycerides in these formulas can be directly absorbed from the small intestine without requiring bile acids. Portoenterostomy (Kasai procedure) is not beneficial and is not recommended for cholestasis. (9) Medications such as ursodeoxycholic acid, cholestyramine, and rifampicin may help with pruritis, but their efficacy varies with each patient. In about 40% of patients with Alagille syndrome, pruritis and xanthomas may be severe and unremitting as to warrant external biliary diversion or liver transplantation.

The clinical course of infants with Alagille syndrome is highly variable. Approximately one-third of patients require liver transplantation, with neonatal cholestasis at presentation associated with worse outcomes. Overall mortality is estimated to be 20% to 30% because of cardiac disease, infection, or progressive liver disease. (7)

Lessons for the Clinician

- Early identification of cholestasis and initiation of a prompt and thorough evaluation are essential for successful treatment and optimal outcomes.
- The differential diagnosis of neonatal cholestasis is broad and includes obstructive, infectious, metabolic, endocrine, and toxic etiologies.
- Cholestasis, cardiac murmur, butterfly vertebrae, renal anomalies, triangular facies, and posterior embryotoxon are among the constellation of symptoms associated with Alagille syndrome.
- Alagille syndrome is caused by a mutation in the *JAG1* or *NOTCH2* gene in more than 90% of cases.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology, clinical manifestations, and differential diagnosis of metabolic and familial causes of cholestasis in the neonate.
- Know the laboratory and imaging features and management of metabolic and familial causes of cholestasis in the neonate.

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Case 2: Conjugated Hyperbilirubinemia in a Late Preterm Neonate

Nicole Flores-Fenlon, Smeeta Sardesai and MS Ed

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3 Emesis in a Term Infant with Dysmorphic Features

Tadarro Lee Richardson Jr., MD,*† Meaghan Ransom, MD, MPH,†
Gabriella Crane, MD,‡ Erin Plosa, MD,§ Jennifer Sucre, MD§

*Department of Internal Medicine; †Department of Pediatrics; ‡Division of Radiology, Department of Pediatrics; and §Division of Neonatology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN

PRESENTATION

A female infant is born at 38 weeks' estimated gestational age to a 23-year-old, gravida 2, para 2 woman. Maternal history is significant for poorly controlled chronic hypertension and limited prenatal care. The woman reports she was returning home from vacation when she experienced painful, frequent contractions, prompting presentation to the nearest emergency department. Her initial blood pressure is 152/102 mm Hg. She has spontaneous rupture of membranes and undergoes repeat cesarean section 3 hours after arrival at the academic medical center.

In the delivery room, Apgar scores are 7 at 1 minute (0 for skin color, and 1 for respiratory effort) and 9 at 5 minutes (1 for skin color). Growth parameters are consistent with a small-for–gestational age infant; the newborn's head circumference, weight, and length are all less than the 1st percentile for gestational age. Initial physical examination is remarkable for upper limb abnormalities, including oligodactyly with the presence of only 2 formed digits on the left upper extremity, a single palpable forearm bone in the left upper extremity, a sacral dimple, significant hirsutism, and abnormal facial features, including synophrys and highly arched eyebrows. She is admitted to the NICU for further care.

In the NICU, she is initiated on feeds of expressed breast milk and colostrum. She passes meconium on the first day after birth. The neonate initially tolerates small volumes of feeds, but by day 2, she experiences nonbilious emesis 15 to 30 minutes after each feed. Intravenous fluids are initiated and a Replogle tube is placed. An abdominal radiograph is obtained on the second day after birth (Fig 1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for recurrent emesis and feeding intolerance in this infant with a nonobstructive bowel gas pattern on the abdominal radiograph includes:

- Gastroesophageal reflux
- Vascular ring or sling
- Duodenal web
- Duodenal stenosis
- Annular pancreas
- Malrotation with or without midgut volvulus
- Extrinsic compression
- Necrotizing enterocolitis

AUTHOR DISCLOSURE Drs Richardson, Ransom, Crane, Plosa, and Sucre have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

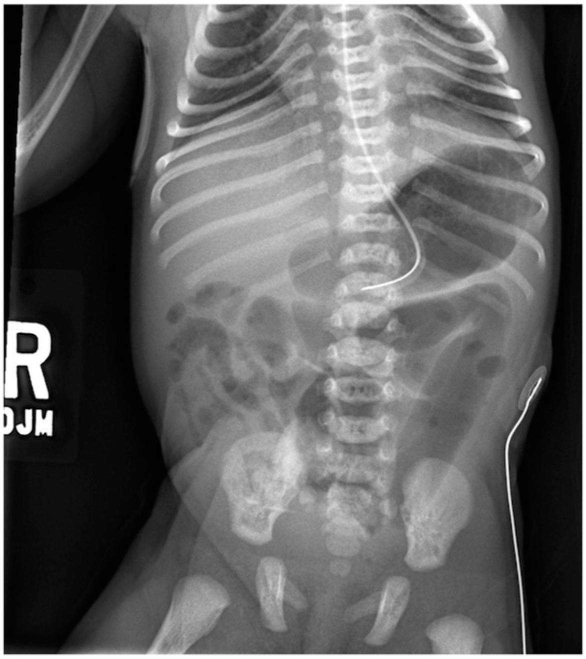


Figure 1. The abdominal radiograph obtained on day 2 after birth demonstrates a non-obstructive bowel gas pattern but with asymmetrical distension of bowel in the left abdomen.

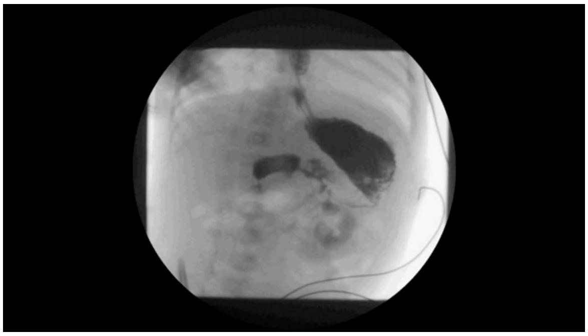
CASE PROGRESSION

The infant continues to have persistent emesis with all feeds. On day 4 after birth, she undergoes a fluoroscopy upper gastrointestinal (GI) series (Video 1, Fig 2). She continues to vomit regularly with feeds, prompting advancement to a nasojejunal tube for enteral nutrition. Her feeding tolerance improves. During this interval, a genetics consultation is obtained, and there is high suspicion for Cornelia de Lange syndrome (CdLS), given the infant's physical examination findings.

On day 11 after birth, the infant develops bilious emesis, prompting surgical consultation; a fluoroscopy upper GI series is repeated (Video 2, Fig 3), which uncovers no evidence of volvulus, but confirms her previously known malrotation. In addition, the study demonstrates an abnormally dilated duodenal bulb with abrupt transition at the D1/D2 junction, concerning for a Ladd band causing intermittent obstruction in this infant.

The infant continues to have projectile emesis, and on day 12 after birth, she is taken to the operating room for Ladd procedure and insertion of a gastrostomy feeding tube. Operative notes report "classic features of intestinal malrotation without volvulus, with significant Ladd bands entrapping the duodenum in the right upper quadrant and retroperitoneum requiring kocherization of the duodenum and division of Ladd bands."

Postoperatively, she tolerates feedings via her gastrostomy tube without difficulty. She remains in the NICU for advancement of feeds and coordination of care before discharge and travel back to the family's home state. The infant is discharged from the NICU 29 days after birth, with close follow-up arranged with her local pediatrician.



Video 1. Upper gastrointestinal series obtained on day 4 demonstrates an anteriorly positioned duodenal sweep and intermittent dilation of the duodenal bulb without fixed narrowing. No evidence of midgut volvulus is seen. Although there is intermittent dilation of the duodenal bulb, there is no evidence of fixed narrowing to suggest duodenal stenosis or extrinsic compression.

Final Diagnosis

The infant is diagnosed as having intestinal malrotation with duodenal obstruction secondary to Ladd bands.

DISCUSSION

CdLS is a well-known syndrome associated with multiple congenital anomalies (cardiac, GI, renal, genital, and ocular), distinct facial features, limb abnormalities, growth

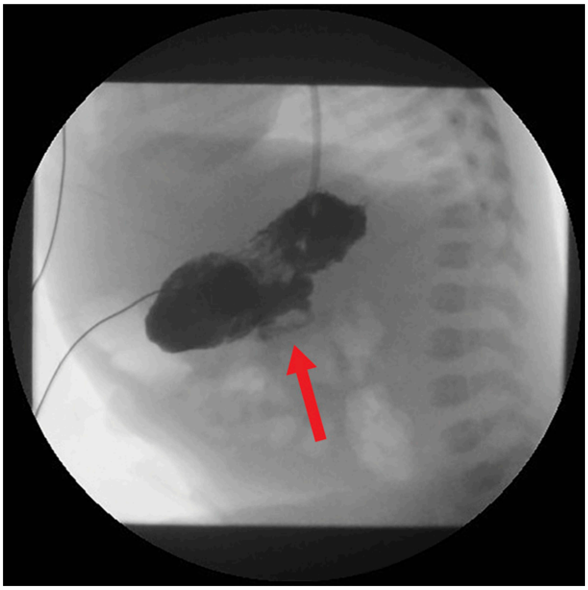
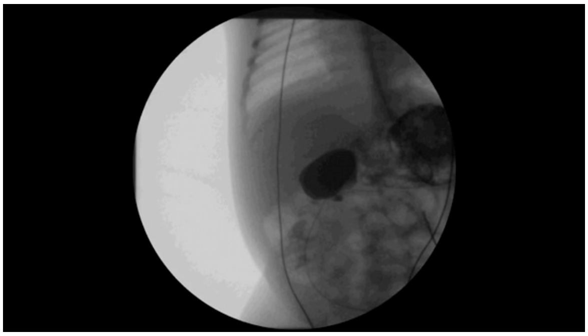


Figure 2. Spot image from the upper gastrointestinal series obtained on day 4 after birth showing the abnormally positioned duodenal sweep far anterior to the spine (arrow).



Video 2. Repeat upper gastrointestinal series 7 days after the initial study, demonstrating severe persistent dilation of the duodenal bulb but with slow passage of contrast through the duodenal sweep into the jejunum, following the course of the nasojejunal feeding tube. Note the inferior displacement of the ligament of Trietz with the tube in place in this infant with known malrotation.

restriction, and developmental delay. (1) A recent consensus statement published by international experts highlights the molecular and clinical features for CdLS in both classic and nonclassic phenotypes. (2) Feeding difficulties and failure to thrive are commonly observed in this patient population. (3)

GI abnormalities are a frequent cause of morbidity and mortality in CdLS, with reflux being the most prevalent GI manifestation. (4) Other associated GI system pathologies include pyloric stenosis, imperforate anus, malrotation with or without volvulus, congenital diaphragmatic hernia, and small-bowel duplication. (2) Although these diseases may vary in their presentation, many are potentially deadly. One study identified the GI system as the second most common cause of mortality in CdLS behind respiratory pathology; specifically, GI-related deaths were most often due to volvulus or obstruction. (5)

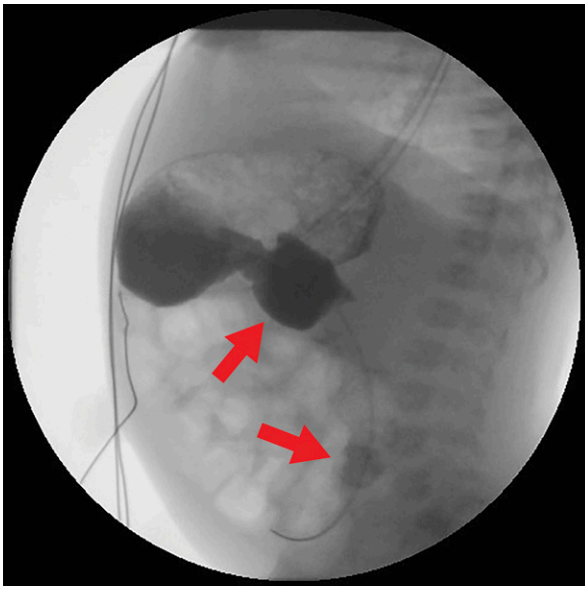


Figure 3. Spot image from the repeat upper gastrointestinal series showing a severely dilated duodenal bulb (upper arrow) and a small amount of contrast moving into the distal duodenum along the feeding tube (lower arrow).

For the current patient, intestinal malrotation presented on day 4 after birth. Malrotation is seen with a higher frequency among patients with CdLS in comparison to the general population; the incidence of symptomatic malrotation was reported to be 5% to 10% in two separate series of patients with CdLS. (6)(7) This incidence is significantly higher than age-matched controls, in which symptomatic malrotation is seen in only 1 in 6,000 live births. (8)

Clinically, our patient initially had projectile, nonbilious emesis, which progressed to bilious emesis on day 11 after birth. This clinical change is attributable to the development of duodenal obstruction from Ladd bands. Fortunately, malrotation in our patient is not complicated by volvulus with small-bowel ischemia, but patients with malrotation are certainly at risk to develop this life-threatening complication. In many cases, malrotation initially presents as one of these acute complications; notably, acute cecal volvulus is the most common presentation of malrotation in patients with CdLS. (5)(6)

As evidenced before, neonates with CdLS are at increased risk of having malrotation, which predisposes them to possible complications such as volvulus or duodenal obstruction. As such, clinicians must have a high index of suspicion for malrotation in any infant with CdLS who develops feeding difficulties, emesis, abdominal distention, or change in behavior or mental status. Appropriate clinical management is prudent in such scenarios, because these infants are at increased risk for morbidity and mortality if not properly identified in a timely manner.

Lessons for the Clinician

- CdLS is a multisystemic syndrome associated with multiple congenital anomalies (cardiac, GI, renal, genital and ocular), distinct facial features, limb abnormalities, growth restriction, and developmental delay. (1)
- Malrotation is a clinically significant finding in CdLS and should be considered in these patients if they present with feeding intolerance.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER association and DiGeorge syndrome).
- Know the etiology, clinical manifestations, diagnosis, and management of GI strictures.

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Intrapartum Challenge of Fetal Growth Restriction

Calvin Lambert, MD,* Kafui Demasio, MD, MPH*
*Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY

ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Lambert and Demasio have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤–10 (–2.0 to –9.0)
Respiratory acidosis	<7.20	>60	Variable	≤–10
Metabolic acidosis	<7.20	<60	Variable	≥–10
Mixed acidosis	<7.20	>60	Variable	≥–10

**Normal ranges from* Obstet Gynecol Clin North Am. *1999;26:695.*

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

  Absent: Amplitude range is undetectable
  Minimal: Amplitude range is greater than undetectable to 5 beats/min
  Moderate: Amplitude range is 6–25 beats/min
  Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes

  – Normal: ≤5 contractions in 10 minutes
  – Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

  – Baseline rate: 110 to 160 beats/min
  – Baseline FHR variability: Moderate
  – Late or variable decelerations: Absent
  – Early decelerations: Present or absent
  – Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol*. 2008;112: 661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

THE CASE

A 21-year-old primigravida woman was admitted to the labor and delivery (L&D) department for a scheduled induction of labor at 39 0/7 weeks of gestation because of a third-trimester diagnosis of intrauterine growth restriction. She began prenatal care at 12 weeks of gestation and had 9 visits before she was transferred to the high-risk obstetrics clinic for an ultrasound finding of fetal growth restriction at 36 3/7 weeks of gestation. The ultrasound examination at the time indicated an estimated fetal weight of 2,141 g, which was lower than the third percentile for gestational age. The amniotic fluid volume, biophysical profile, and Doppler indices were all within normal limits. She had initial dating ultrasonography at 16 1/7 weeks of gestation when the fetal biometry findings were consistent with her last menstrual period date, and subsequent fetal measurements at the anatomic survey and at 29 0/7 weeks of gestation were both consistent with her dating ultrasonography findings. Because there was a 3-week lag in the fetal interval growth, the team planned for an induction.

The prenatal course was significant for the use of marijuana confirmed with 2 positive urine drug screens early in her prenatal care. The last urine drug screen at the time of admission to L&D was negative. Except for mild anemia (hemoglobin of 10.1 g/dL [101 g/L]), the remainder of the medical, surgical, and psychosocial histories were unremarkable.

Upon arrival at L&D for her induction of labor, the fetal heart rate (FHR) tracing was reactive without evidence of labor contractions (Fig 1), and considered to be a category 1 tracing. All vital signs were within normal limits, and her blood pressure was 131/61 mm Hg. Vaginal examination revealed an unfavorable cervix that permitted a fingertip, and was 50% effaced with the vertex at −3 station. The labor induction was started with 25 μg of vaginal misoprostol for cervical ripening, and the FHR tracing remained category 1 throughout this process. After 4 hours, she was reexamined and the cervix was 3-cm dilated, 80% effaced, and at 0 station, and she requested epidural analgesia which was provided. Audible FHR decelerations to a nadir of 80 beats/min from a baseline of 150 beats/min soon became apparent. The FHR tracing became discontinuous immediately after epidural analgesia was completed. Intrauterine resuscitative measures with intravenous fluid bolus, maternal repositioning, and oxygen by nonrebreather face mask were initiated. The blood pressure at that time was 100/60 mm Hg, and after approximately 10 minutes, a category 2 FHR tracing was reestablished and demonstrated fetal tachycardia with decelerations (Fig 2). For the next 30 minutes, the tracing continued to exhibit decelerations (Figs 3 and 4) leading to the interventions of artificial rupture of membranes that produced meconium-stained amniotic fluid, and placement of a fetal scalp electrode and an intrauterine pressure catheter to better elucidate contractions. During these interventions, a series of 3 subcutaneous tocolytic injections were administered for suspected tachysystole. Finally the tracing became category 1 as shown in Fig 5. Cervical examination at this time revealed that it was 5-cm dilated, 80% effaced, and the presenting part at 0 station. A positive response to scalp stimulation was elicited (arrow in Fig 5). These findings were reassuring that the fetus was not hypoxic after the extended episode of abnormal FHR patterns. After a couple of hours, oxytocin was started to further augment her labor, but stopped within an hour because of prolonged deceleration (Fig 6). She was examined and found to be fully dilated, 10 cm, and the vertex was at +2 station, which began her second stage of labor. As soon as she started pushing, the intrauterine pressure catheter became dislodged (Fig 7) and the FHR tracing developed recurrent variable decelerations (Fig 8). Fortunately, the second stage of labor lasted only 32 minutes for this nulliparous woman and a viable female infant with a birthweight of 2,230 g was delivered vaginally. The Apgar score was 8 and 9 at 1 and 5 minutes, respectively. The umbilical cord blood gases are shown in Table 2. The placental pathology revealed a mature placenta that was below the 10th percentile for weight for gestational age with villous hypoplasia and multiple villous infarcts. The fetal membranes did not reveal any histopathologic abnormalities, and the umbilical cord showed 3 vessels.

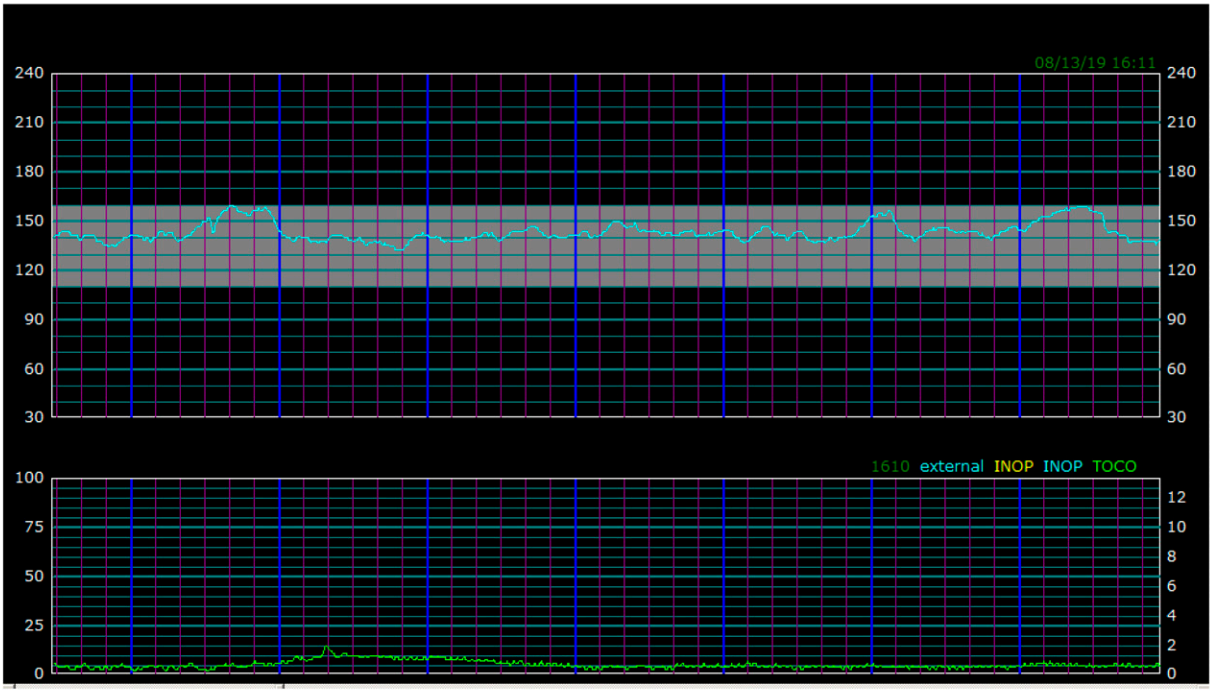

Figure 1. Electronic fetal monitoring strip 1.

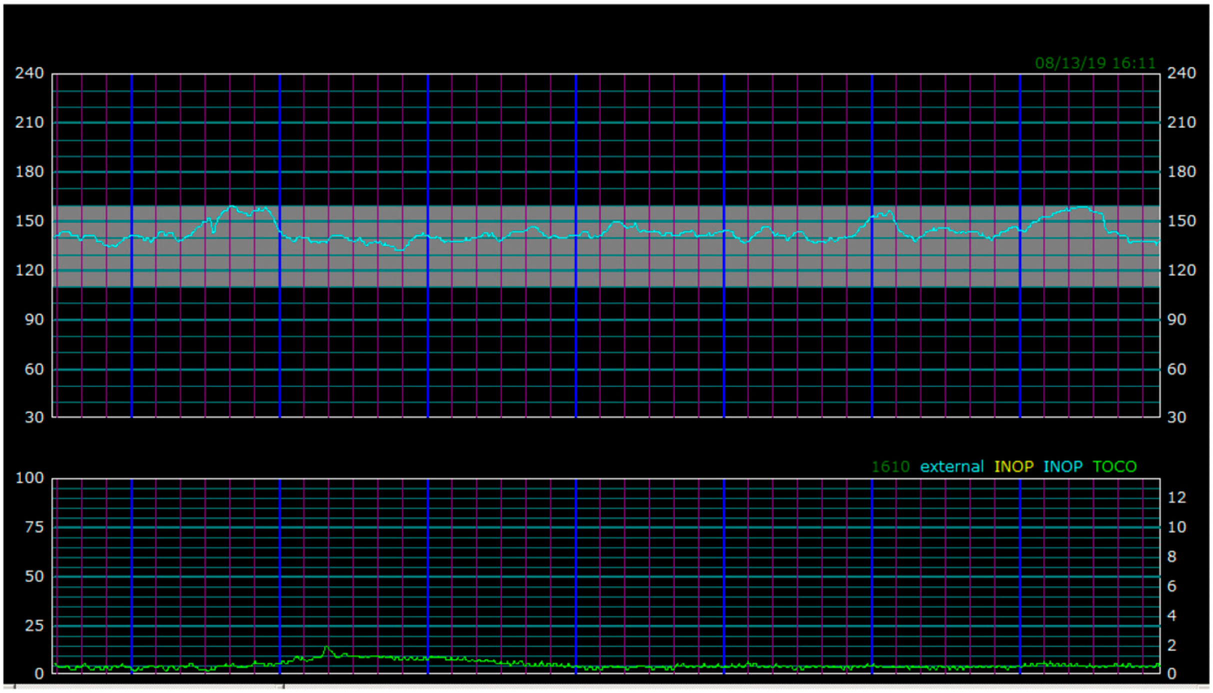

Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows (Fig 1):

- Baseline rate: 140 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Reactive or category I
- Differential diagnosis: Reactive and reassuring fetal heart tracing
- Action: None

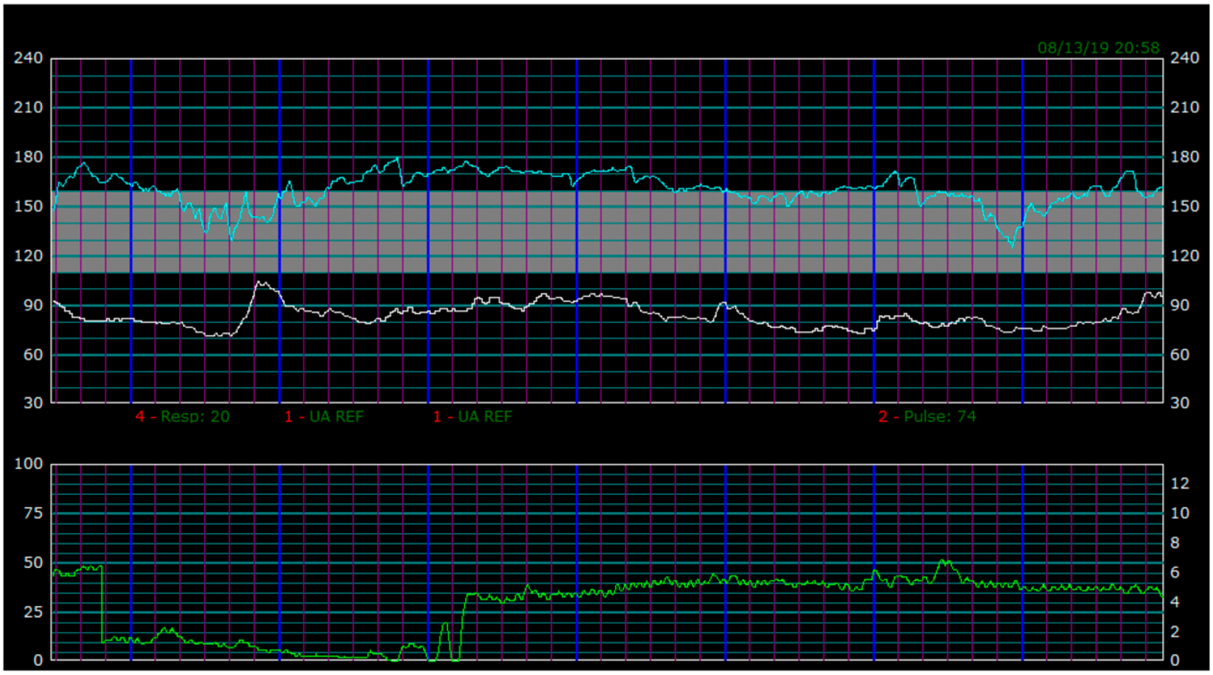

Figure 2. Electronic fetal monitoring strip 2.

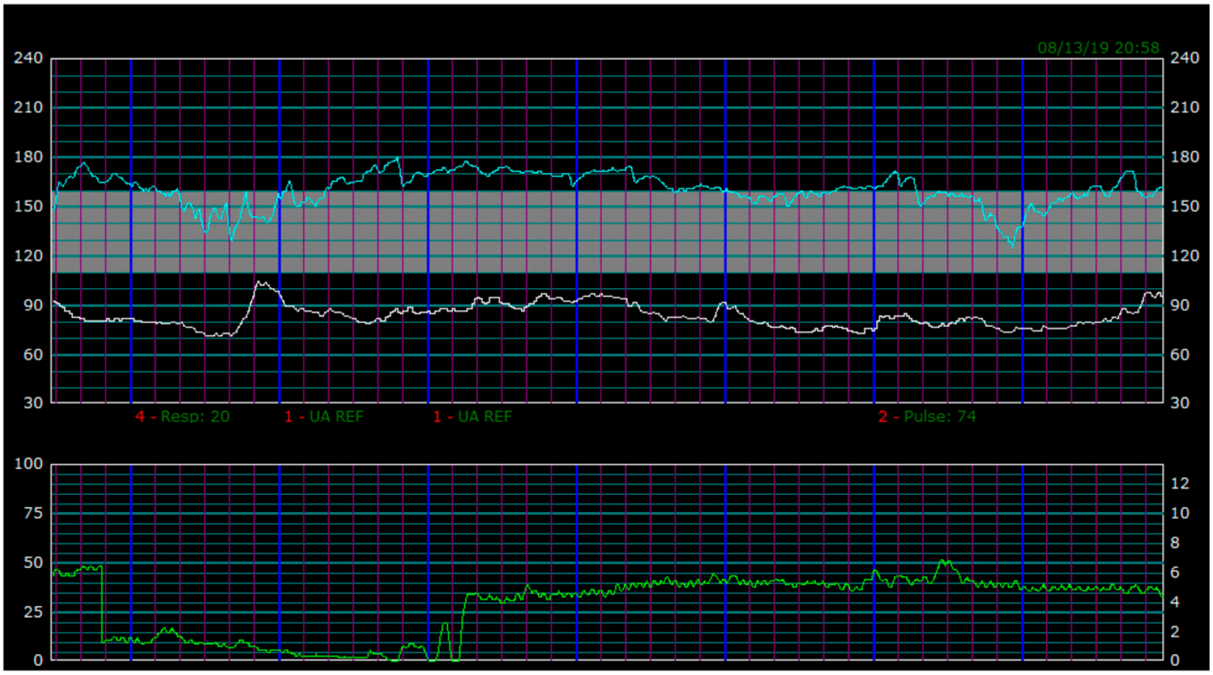

Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows (Fig 2):

- Baseline rate: 170 beats/min
- Baseline variability: Moderate
- Episodic patterns: Decelerations (contractions are not present)
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Maternal hypotension from epidural analgesia
- Action: Intrauterine resuscitation

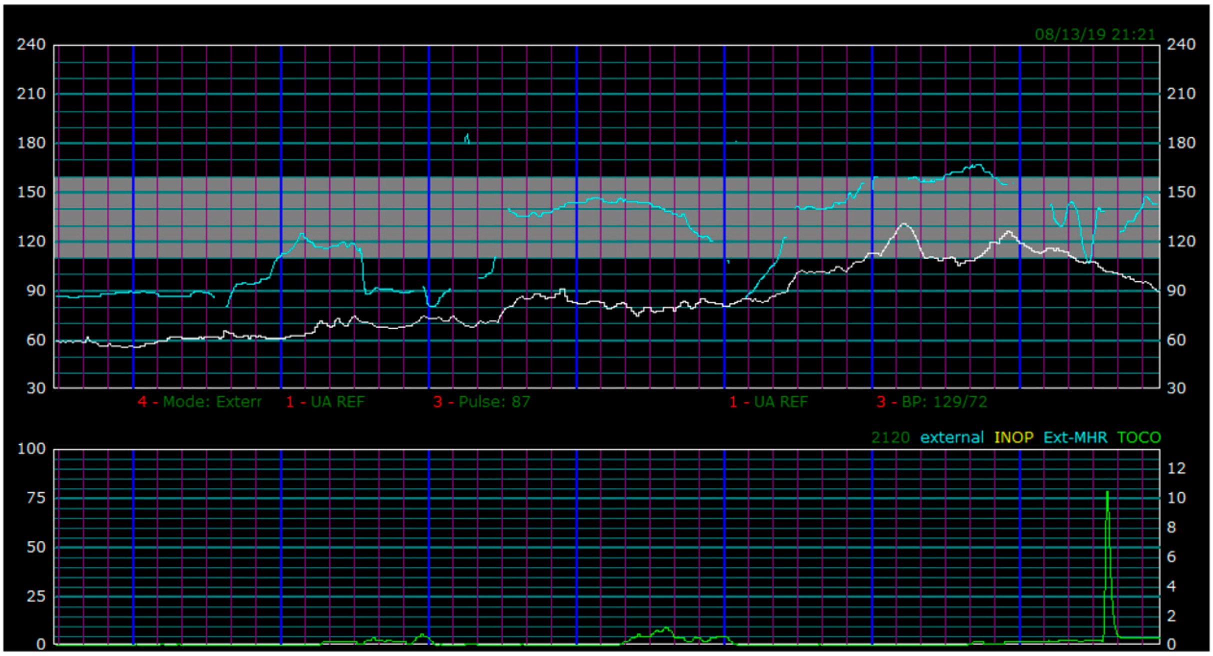

Figure 3. Electronic fetal monitoring strip 3.

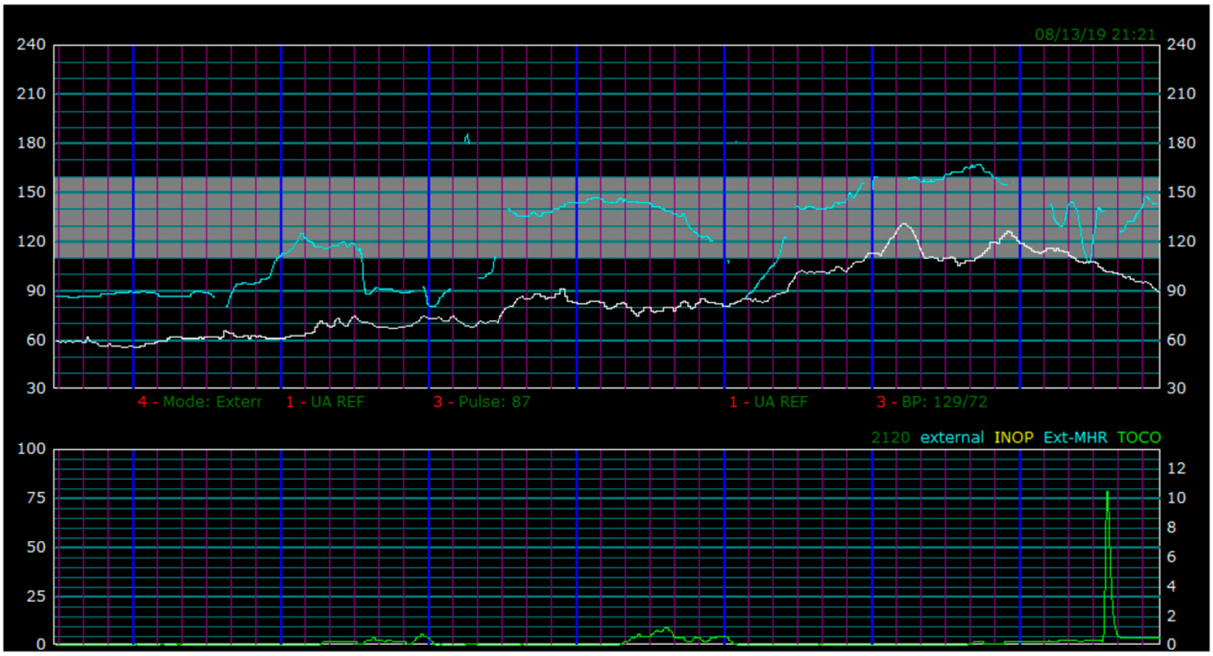

Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows (Fig 3):

- Baseline rate: 90 beats/min (increased to 140 beats/min)
- Baseline variability: Minimum, later segment appears moderate, but is discontinuous
- Episodic patterns: Decelerations, appear variable with sharp drop from baseline
- Periodic patterns: None (contractions are not present)
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Developing category III tracing, fetal hypoxia, versus the continuous effect of epidural
- Action: Ongoing fetal resuscitation, placement of internal fetal monitor (fetal scalp electrode)

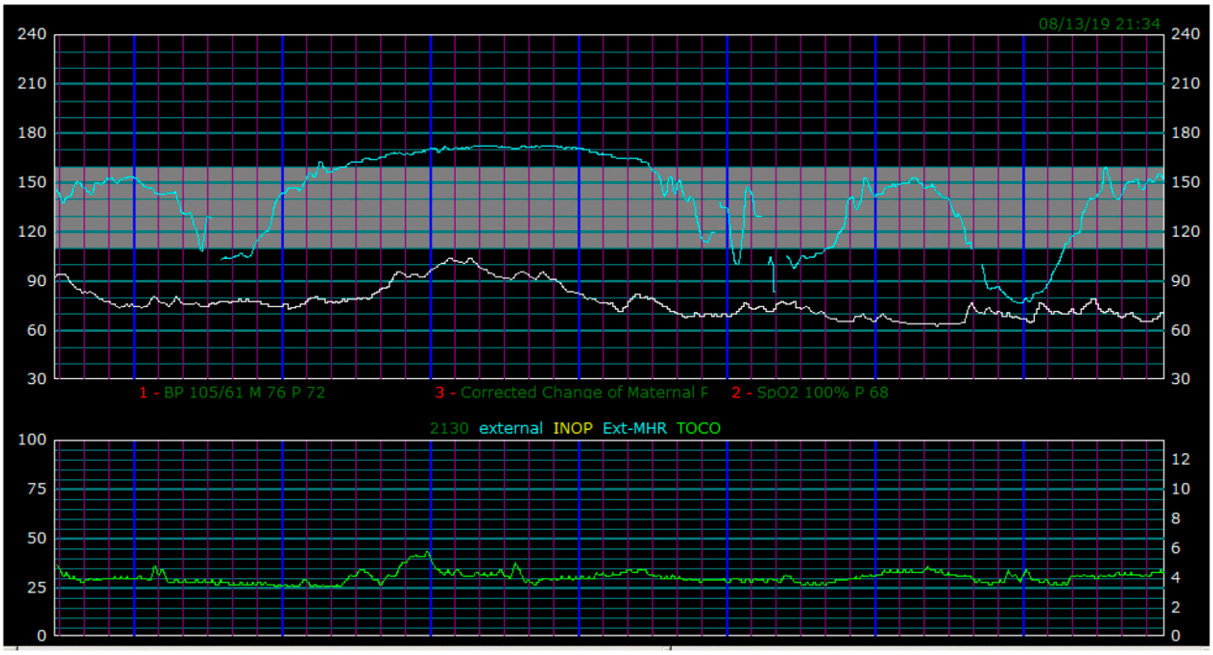

Figure 4. Electronic fetal monitoring strip 4.

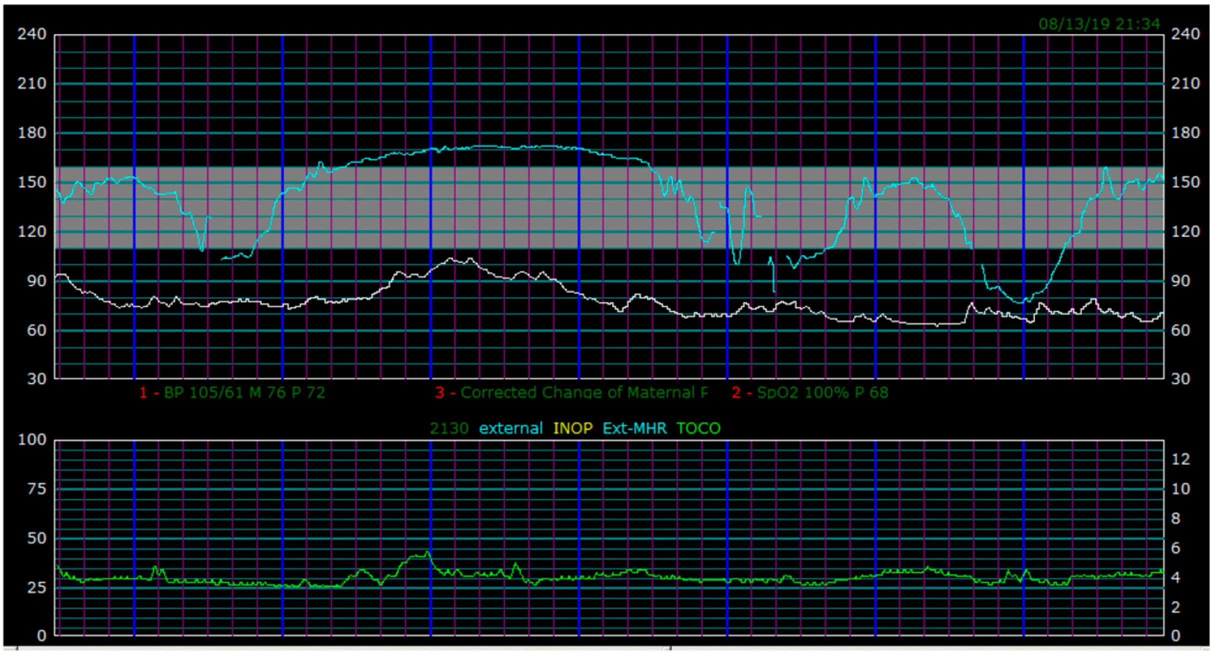

Figure 4. Electronic fetal monitoring strip 4.

Findings from EFM strip 4 are as follows (Fig 4):

- Baseline rate: 170 beats/min
- Baseline variability: Minimum and moderate (at the beginning and end of the panel)
- Episodic patterns: Recurrent variable decelerations
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Developing category III, risk of fetal hypoxia
- Action: Intrauterine pressure catheter, ongoing fetal resuscitation, plan for delivery if no improvement

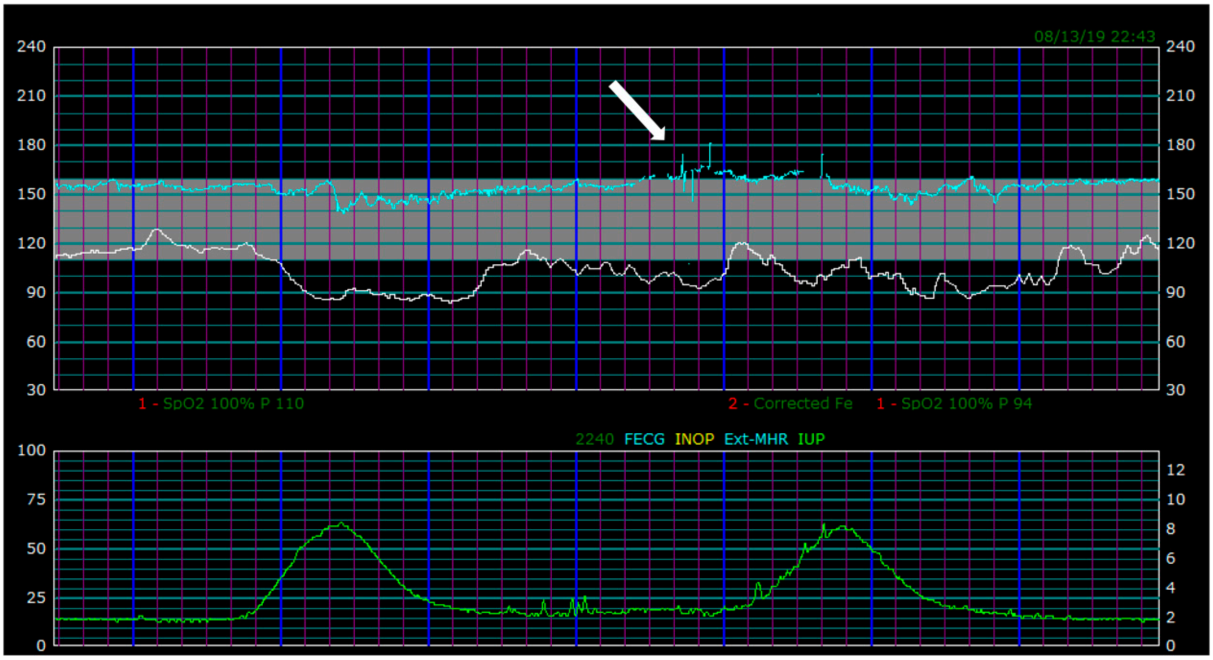

Figure 5. Electronic fetal monitoring strip 5.

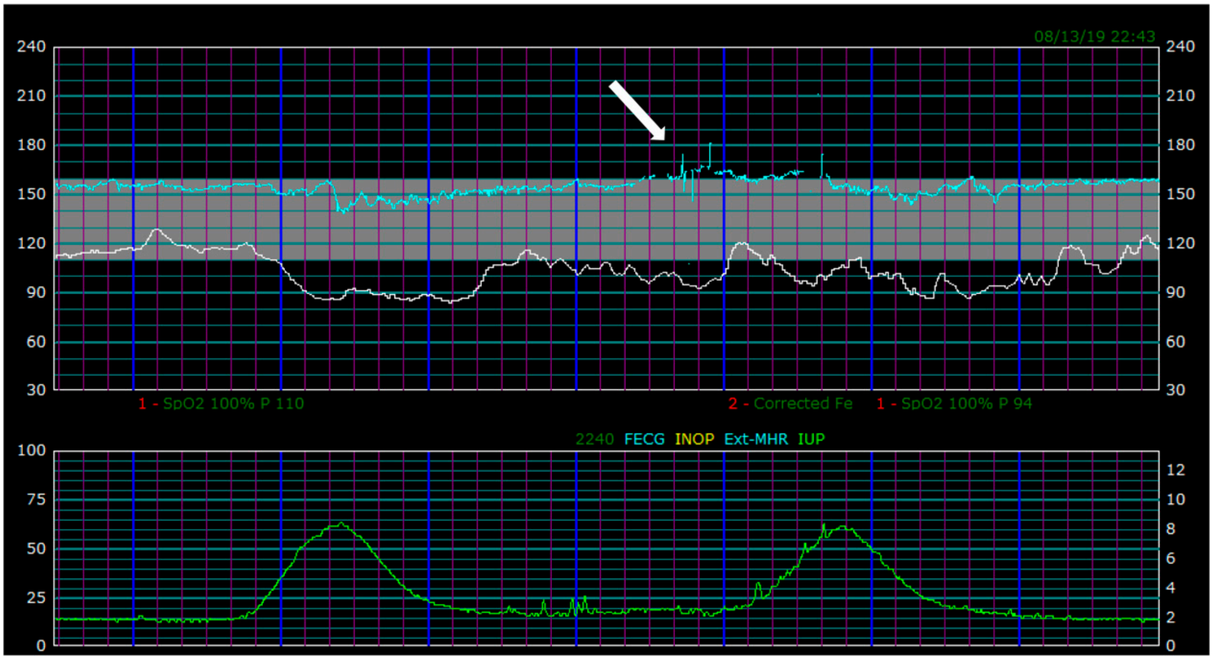

Figure 5. Electronic fetal monitoring strip 5.

Findings from EFM strip 5 are as follows (Fig 5):

- Baseline rate: 155 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: 3 minutes apart
- Interpretation: Category I
- Differential diagnosis: Positive response to scalp stimulation before second contractions; fetal pH is >7.2; fetus is not acidotic
- Action: None

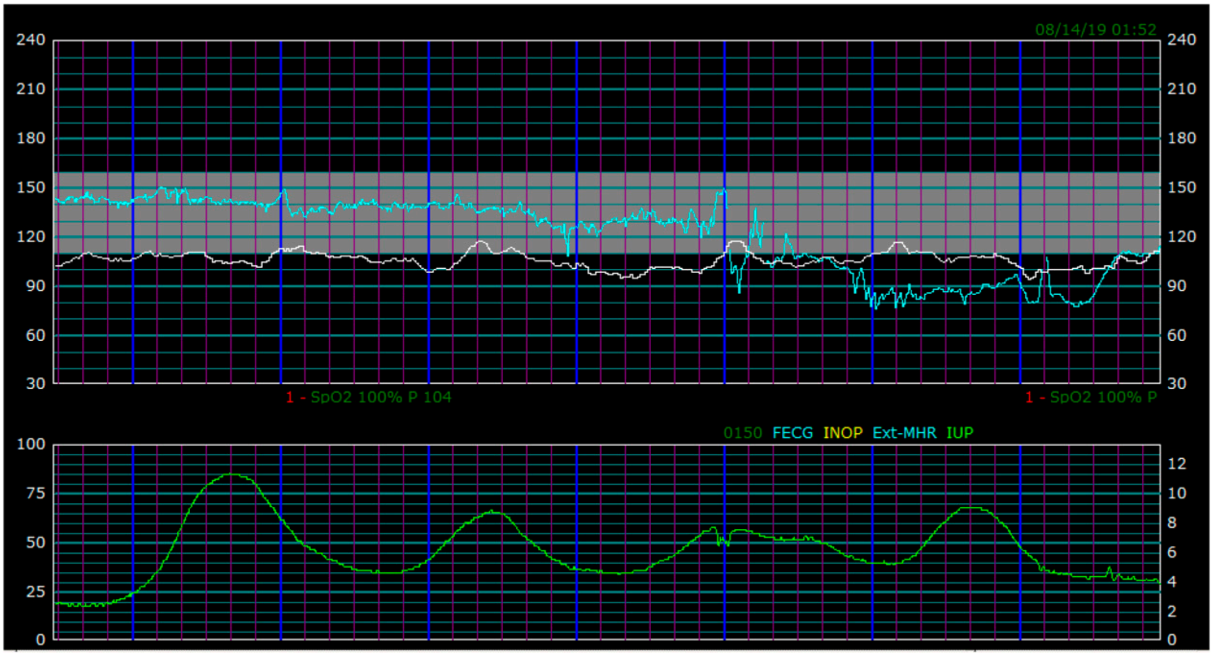

Figure 6. Electronic fetal monitoring strip 6.

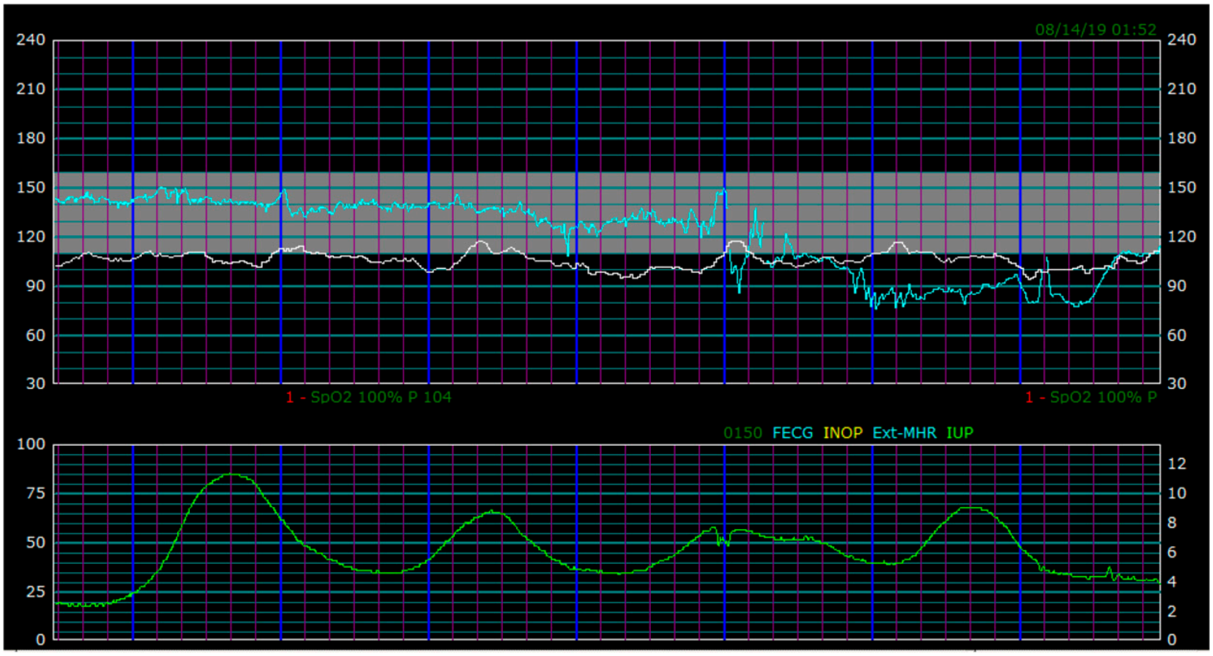

Figure 6. Electronic fetal monitoring strip 6.

Findings from EFM strip 6 are as follows (Fig 6):

- Baseline rate: 140 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: Prolonged deceleration
- Uterine contractions: Every 2 minutes
- Interpretation: Category II
- Differential diagnosis: Cord compression, fetal descent
- Action: Repositioning

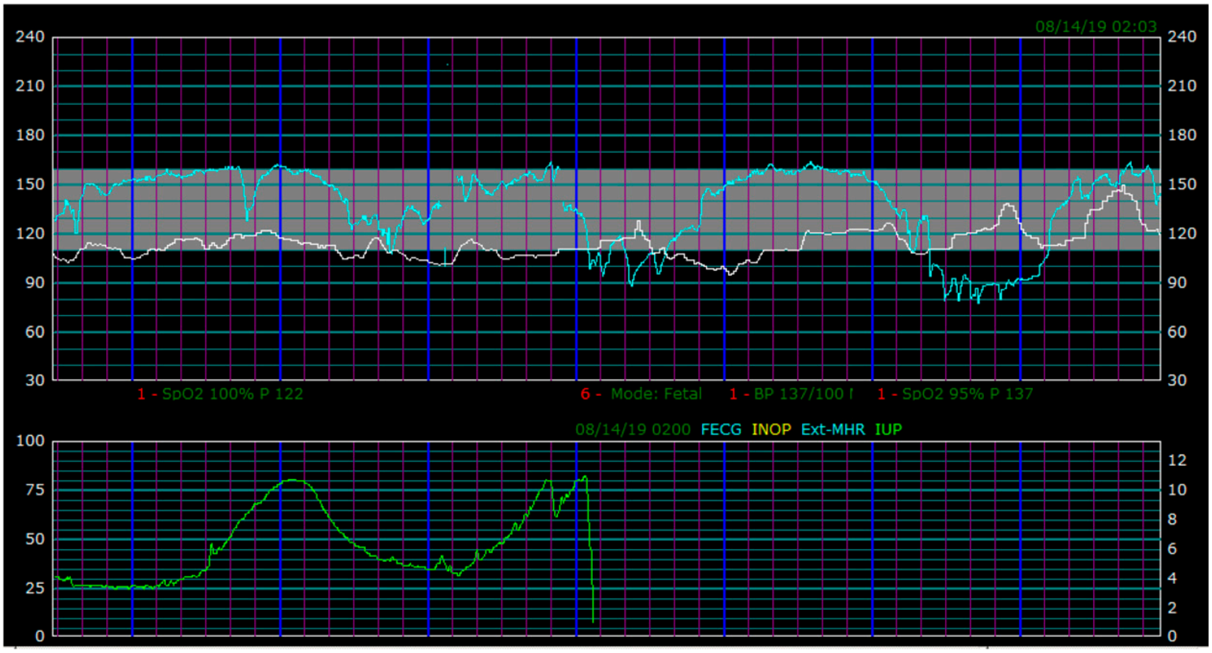

Figure 7. Electronic fetal monitoring strip 7.

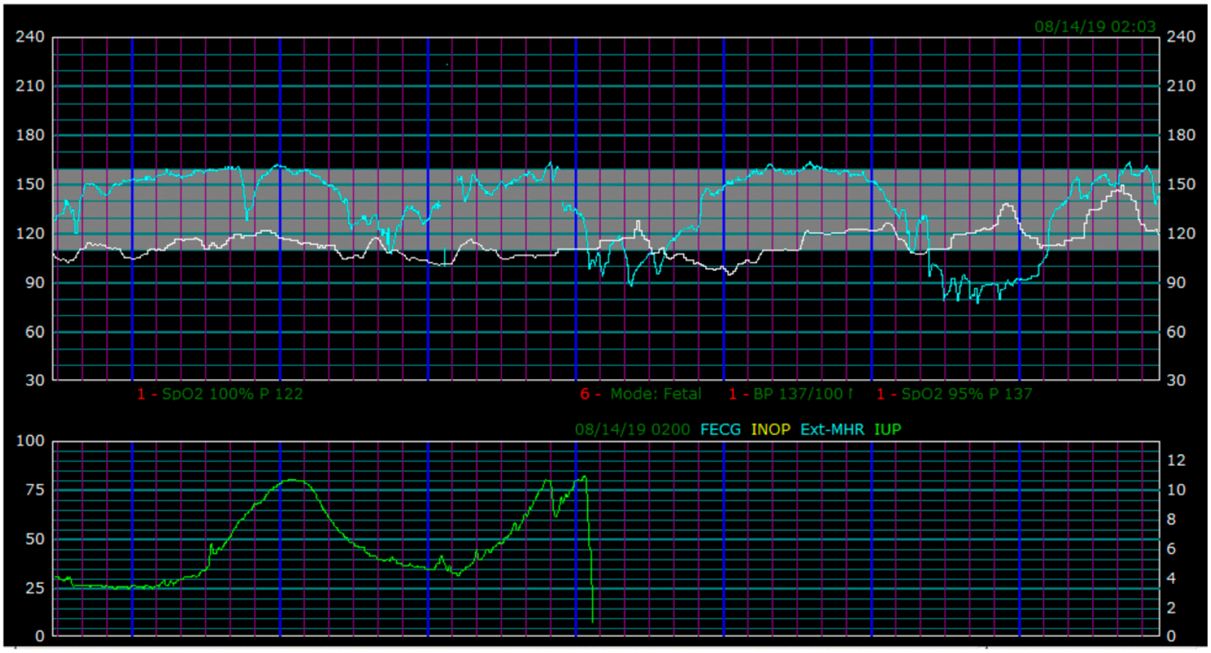

Figure 7. Electronic fetal monitoring strip 7.

Findings from EFM strip 7 are as follows (Fig 7):

- Baseline rate: 160 beats/min
- Baseline variability: Minimum
- Episodic patterns: None
- Periodic patterns: Late deceleration after first contraction and then variable decelerations with loss of internal pressure catheter monitor
- Uterine contractions: 2 minutes apart
- Interpretation: Category II
- Differential diagnosis: Cord compression, fetal descent, developing hypoxia
- Action: Repositioning, amnioinfusion, intrauterine resuscitation, prepare for delivery

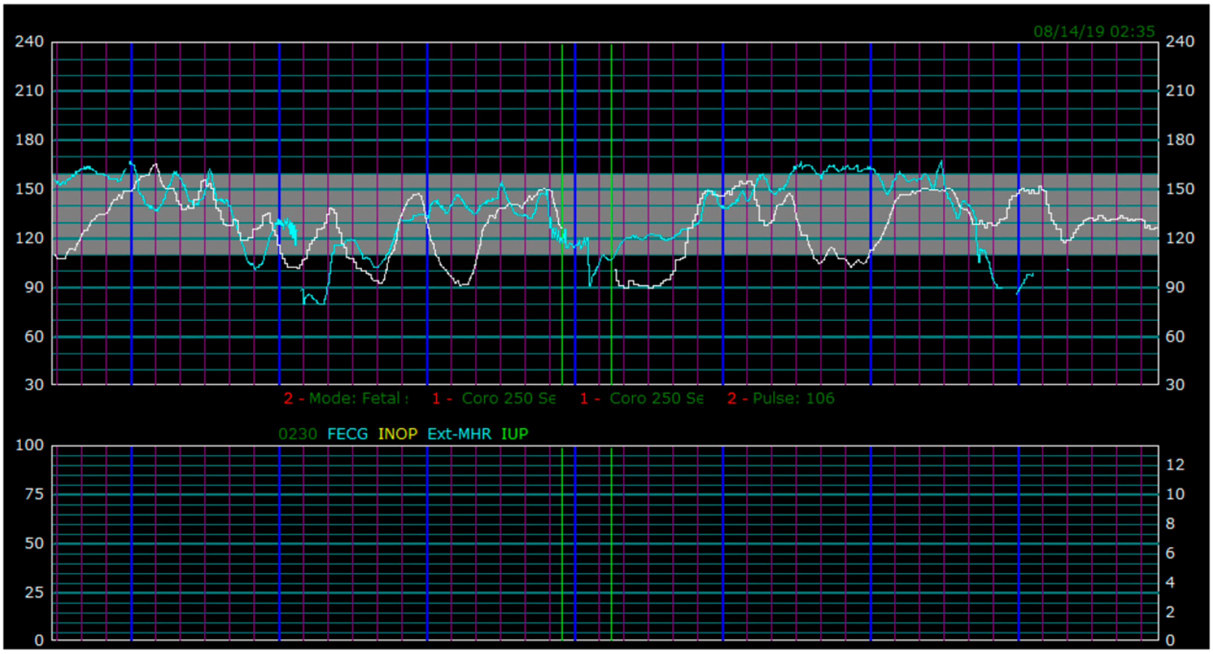

Figure 8. Electronic fetal monitoring strip 8.

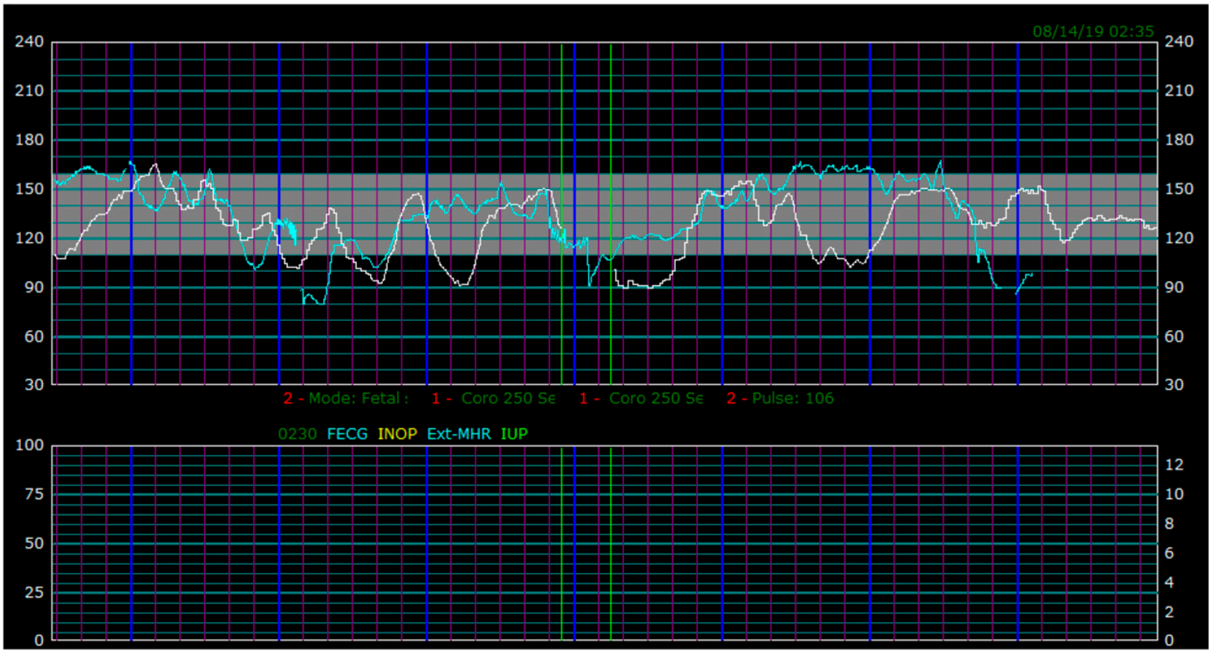

Figure 8. Electronic fetal monitoring strip 8.

Findings from EFM strip 8 are as follows (Fig 8):

- Baseline rate: 160 beats/min
- Baseline variability: moderate
- Episodic patterns: Recurrent variable decelerations (contraction monitoring is absent, but uterine activity is likely still occurring)
- Periodic patterns: None
- Uterine contractions: Absent (monitor is loss)
- Interpretation: Category II
- Differential diagnosis: Cord compression
- Action: Repositioning, avoid pushing with every contraction to allow intrauterine fetal resuscitation

DISCUSSION

Intrauterine growth restriction (IUGR), also referred to as *fetal growth restriction* (FGR), describes a state of pathologic fetal growth suspected antenatally if ultrasonography demonstrates the fetal biometry below the 10th percentile for gestational age. The cause of IUGR may be an intrinsic fetal or placental issue, related to maternal medical conditions that affect the fetal growth, or may result from a combination of these factors. The majority of FGR is detected in the third trimester by lagging fetal growth of a structurally normal-appearing fetus and may occur in an otherwise uncomplicated gestation. This type of presentation raises the concern about placental integrity and the associated increased risk of poor pregnancy outcomes such as stillbirth or neonatal morbidity and mortality. (1)

Experts agree that late-onset growth restriction occurs when the onset is after more than 32 weeks of gestation. (2) It is characterized by uteroplacental dysfunction that often leads to fetal intolerance of labor and an increased rate of cesarean delivery. Differentiating a constitutionally small,

TABLE 2. **Umbilical Cord Blood Gases for the Neonate**

ARTERIAL	NEONATE	REFERENCE RANGE
pH	7.07	7.35 to 7.45
P_{CO_2}, mmol/L	78	35.0 to 45.0
P_{O_2}, mmol/L	18	80 to 100
Base excess	−7.30	−9.00 to −2.00
Bicarbonate, mmol/L	22	22.0 to 28.0

but normal fetus, from one that has a compromised placenta has been the focus of extensive research using Doppler interrogation of various aspects of the fetal cardiovascular circulation. An abnormal Doppler cerebroplacental ratio, also known as "brain sparing," is likely the most predictive assessment for adverse perinatal outcome. (3)

The intrapartum course of a growth-restricted fetus as a result of uteroplacental insufficiency can be challenging because, in most cases, the acid-base status has a lower venous pH and higher carbon dioxide compared with appropriately grown fetuses, indicating a baseline acidosis before the onset of labor. (4) The stress of labor is precipitated by interruption of placental perfusion from uterine contractions, thereby limiting oxygen delivery and the exchange of gases. This interruption is less tolerated by the fetus because of very little reserve. Partly evidenced by this case, insults such as maternal hypotension after epidural placement can result in abnormal FHR changes, the risk of meconium aspiration syndrome, and cesarean delivery.

One question raised by this case of a seemingly healthy pregnancy with severe growth restriction at 39 weeks of gestation, is: "what role does intrauterine exposure to cannabis play in the development of IUGR?" Survey data report that 3.4% of pregnant women of 15 to 44 years of age used marijuana, making it the most common illicit substance used in pregnancy. Several studies indicate an association between intrauterine exposure to cannabis and FGR. A recent Ontario-based population investigation of over 600,000 women included 9,427 (1.4% of the population) self-reported marijuana users. The study compared cannabis users with nonusers for adverse pregnancy outcomes and reported an increased risk for small size for gestational age at the third (relative risk 2.6) and 10th (relative risk 1.96) percentiles for women who reported use of cannabis in pregnancy. They also reported a significant association with preterm birth. (5) One literature compilation on the health effects of prenatal, perinatal, and neonatal exposure to cannabis is by the National Academies of Sciences, Engineering, and Medicine. (6) This publication is based on committee analysis of studies primarily after 1999 and was funded by various national and state sources. Although they report an association of FGR with cannabis, the same was not found for preterm birth. They discuss the biologic plausibility of noncannabinoid substances in "smoked cannabis and cigarette smoking" that increases carbon monoxide and blood levels of carboxyhemoglobin. The mechanism of FGR is thought to be hypoxia resulting from a shift in the oxyhemoglobin curve that is caused by carbon monoxide. The development of growth restriction is likely dose dependent and occurs over time. The report points out the limitations of research studies such as 1) cannabis use is exclusively self-reported with lack of biological validation, 2) cannabis exposure was almost exclusively through smoking and often confounded by the use of other substances, and 3) the potency of cannabis varied across time. (6) The quality of the research is likely not going to change because cannabis is an illicit substance, and constructing a prospective randomized study is seemingly impossible.

Our case demonstrates that FGR in a seemingly uncomplicated gestation can be associated with significant FHR abnormalities that typically involve late decelerations because of uteroplacental insufficiency. However, prolonged decelerations, variable decelerations, and tachycardia are tracing patterns that may also be seen. Close attention to the labor course is imperative and constant reassessment of fetal well-being is necessary to prevent fetal acidosis. In this case, a vaginal delivery was obtained because of the relatively fast progression of labor; however, the majority of growth-restricte fetuses will require cesarean delivery.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the differential diagnosis and management of maternal hypotension in labor and its effect on the fetus.
- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor including reassuring and nonreassuring and indeterminate patterns.
- Know the effects on the fetus and/or newborn infant of maternal substance abuse (eg heroin, cocaine, cannabis, methamphetamines, tobacco).
- Know how to evaluate fetal growth rate and fetal growth restriction and the management of fetal growth restriction.

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NeoReviews 2020;21;e131
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A Newborn with a Large Posterior Head Mass

Whitney D. Ficker, MD,* Linda Dunscombe, NNP,* Naomi Lauriello, MD,* Akshaya J. Vachharajani, MD*

**Department of Child Health, Women's and Children's Hospital and University of Missouri Healthcare, Columbia, MO*

THE CASE

A preterm newborn presents with a large posterior head mass.

Prenatal and Birth Histories

- Born to a 24-year-old gravida 1 white woman.
- Medical history significant for obesity (body mass index 39 kg/m^2), depression, anxiety, bipolar disorder, and methamphetamine use 2 years ago. She was not taking any prescription medications or vitamins at the beginning of the pregnancy.
- Prenatal course was significant for daily marijuana use. Ultrasonography performed at 23 weeks' gestation showed a large occipital fetal mass and bilateral ventriculomegaly. Microarray revealed a normal female genotype. A fetal echocardiogram was normal. Fetal head magnetic resonance imaging (MRI) at 28 weeks' gestation showed a low occipital defect with a skin-covered posterior sac containing cerebrospinal fluid (CSF) without internal brain tissue (Fig 1, blue arrow). MRI also showed findings suggestive of partial/complete agenesis of the corpus callosum and a dysplastic appearance of the cerebellum and pons. A guarded prognosis for survival, even with surgical intervention, was discussed during prenatal counseling. Parents leaned toward palliative care but chose to make the final decision after the infant's birth.
- The pregnancy was also complicated by gestational diabetes mellitus diagnosed at 30 weeks. Maternal treatment with insulin was initiated at 33 weeks' gestation because of persistent hyperglycemia. The woman also experienced worsening bipolar disorder during pregnancy and was started on quetiapine treatment.
- Prenatal maternal laboratory findings were: Group B *Streptococcus*—negative; human immunodeficiency virus—nonreactive; rapid plasma reagin—nonreactive; hepatitis B surface antigen—nonreactive; rubella—immune; spinal muscular atrophy carrier status—positive.
- Spontaneous rupture of membranes occurred at 33 5/7 weeks' gestation. Upon admission, the woman was noted to be hypertensive and was diagnosed with preeclampsia without severe features. She received 1 dose of betamethasone before delivery. Regular contractions were noted with cervical change to 6 cm, and the decision was made to proceed with cesarean delivery to avoid birth trauma because of the posterior head mass. The neonatal team was consulted to evaluate the infant before proceeding with palliative care.
- Estimated gestational age: 33 6/7 weeks.
- Apgar scores: 8 and 9 at 1 and 5 minutes, respectively.

NOTE The editors and staff of *NeoReviews* find themselves in the fortunate position of having too many submissions for the *Visual Diagnosis* feature. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will resume accepting new cases on August 1, 2020. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

AUTHOR DISCLOSURE Drs Ficker, Lauriello, Vachharajani and Ms Dunscombe have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

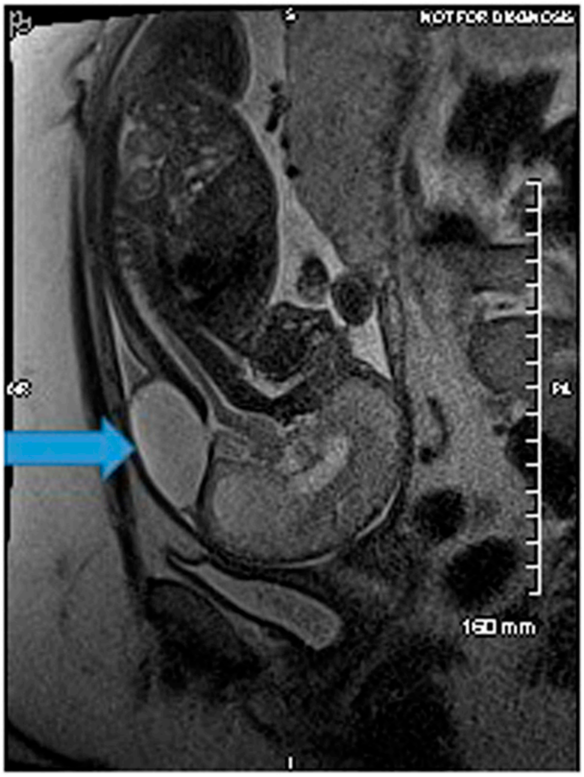

Figure 1. Fetal head magnetic resonance imaging scan at 28 weeks' gestation showing a low occipital defect with a skin-covered posterior sac containing cerebrospinal fluid without internal brain tissue (blue arrow).

Presentation

At birth, the posterior head mass appeared intact and was covered with skin. No other physical malformations were noted. The infant was initially positioned laterally to avoid pressure to the mass. Suprasternal retractions were noted, suggestive of airway occlusion, so the infant's body was elevated on blankets and the head was supported, allowing for the proper "sniffing" position.

Continuous positive airway pressure (CPAP) was initiated at 3 minutes after birth because of respiratory distress. Bag and mask efforts were abandoned because of positioning challenges. The infant appeared comfortable while receiving CPAP and was transferred to the NICU.

PROGRESSION

Vital Signs

- Heart rate: 133 beats/min
- Respiratory rate: 26 breaths/min with nasal CPAP of 5 cm H_2O
- Blood pressure: 65/34 (mean 44) mm Hg
- Oxygen saturation: 99% in room air CPAP
- Temperature: 99.0°F (37.3°C)

Physical Examination (Day 1)

- Birthweight = 2.40 kg (77th percentile); length = 42.5 cm (31st percentile); head circumference = 29.0 cm (15th percentile)
- Head: Large posterior head mass originating from the base of the skull (Fig 2). Head mass fully transilluminated (Fig 3). Full but soft, large anterior fontanelle. Symmetric facies. Patent nares.
- Eyes: Extraocular movements intact. Pupils equal, round, and reactive to light.
- Oral cavity: Oral mucosa moist. Palate intact.
- Lungs: Lungs clear to auscultation bilaterally. Respirations nonlabored. No stridor. Symmetrical chest wall expansion. Nasal cannula in place.
- Cardiovascular: Regular rate and normal rhythm. No murmur. Good pulses equal in all extremities. Normal peripheral perfusion.
- Abdomen: Soft, nontender, nondistended. Normal bowel sounds. No organomegaly.
- Genitourinary: Normal female genitalia. Patent anus.
- Skeletal: Spine appears normal with overlying intact skin. No sacral dimple.
- Skin: Warm, dry, pink. No visible rash.
- Neurologic: Normal response to stimulation. Spontaneous movement of all extremities. Normal sucking and swallowing. Gag reflex present. Moro, palmar, plantar, rooting, and Babinski reflexes all present.

Laboratory Studies

- White blood cell count: $13.58\times10^3/\mu L$ ($13.58\times10^9/L$) with 66% neutrophils, 5% bands, and 14% lymphocytes
- Red blood cell count: $4.84\times10^3/\mu L$ ($4.84\times10^9/L$)
- Hemoglobin: 17.6 g/dL (176.0 g/L)
- Platelet count: $244\times10^3/\mu L$ ($244\times10^9/L$)
- Blood glucose: 71 mg/dL (3.9 mmol/L)
- Capillary blood gas: pH 7.299, Pco_2 54.8 mm Hg (7.2 kPa), Po_2 54.6 mm Hg (7.3 kPa), bicarbonate 26.1 mEq/L (26.1 mmol/L), base excess 0.4 mEq/L

Radiographic Studies

A postnatal brain MRI scan was obtained (Figs 4 and 5).

DIFFERENTIAL DIAGNOSIS

- Cranial encephalocele
- Cranial meningocele
- Cystic hygroma
- Epidermoid or dermoid cyst
- Hemangioma

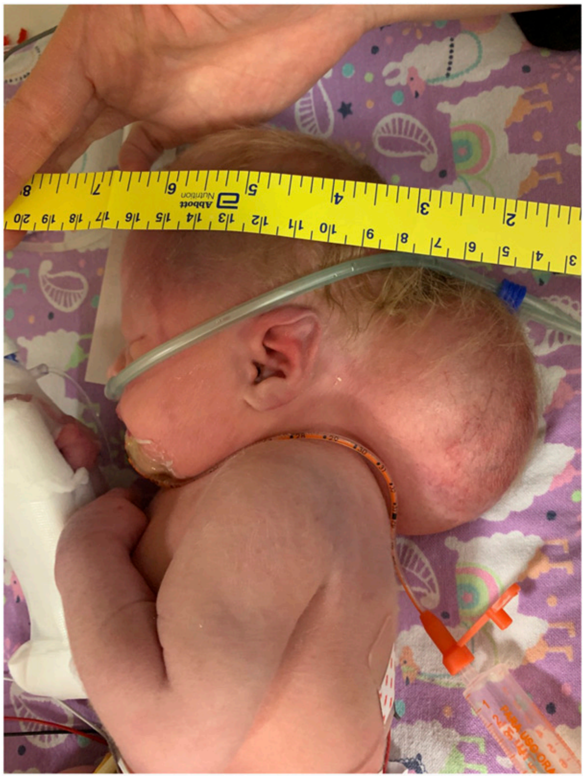

Figure 2. The patient with a large posterior head mass originating from the base of the skull.

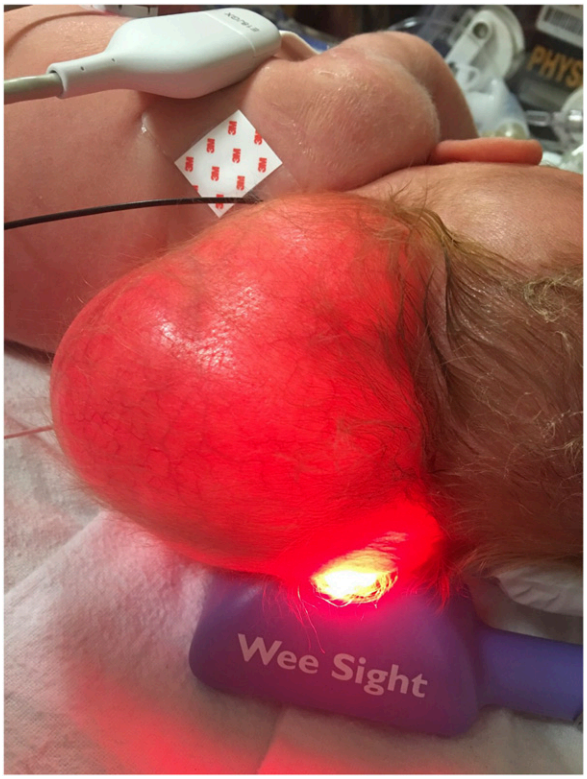

Figure 3. The patient's head mass was able to be transilluminated.

- Lipoma
- Teratoma

ACTUAL DIAGNOSIS

Cranial (Occipital) Encephalocele

The infant's initial physical examination did not reveal significant findings apart from the large posterior head mass; no neurologic abnormalities were observed. Full transillumination of the head mass and its location favored cranial meningocele rather than cranial encephalocele despite the prenatal MRI findings showing a mass in the lower occipital region.

An MRI of the brain and spine was completed on day 1 of age (Figs 4 and 5), which revealed a low occipital/high cervical encephalocele (Fig 4, blue arrow) with associated craniocervical defect and partial herniation of the cerebellar vermis through the osseous defect (Figs 4 and 5, red arrows). The latter findings were suggestive of Chiari malformation type III. In addition, the cerebellum (Fig 5, yellow arrow) and brainstem appeared dysplastic, with kinking at the cervicomedullary junction. It is worth noting that these imaging findings were not associated with clinical findings suggestive of cranial nerve palsy. Supratentorial moderate ventriculomegaly (Fig 5, blue arrow) with colpocephalic appearance of the occipital horns of the lateral ventricle was noted. No evidence of spinal dysraphism was seen.

Management

Given the infant's reassuring clinical status after birth, the parents elected to pursue any intervention necessary. Upon admission to the NICU, the infant continued to receive CPAP. Evaluation of the infant included renal ultrasonography, echocardiography, and an ophthalmologic examination, results of which were all normal. The infant was able to transition to room air without respiratory support within 48 hours of age. On day 6 of age, the encephalocele was noted to have increased in size and appeared under tension with a firmer anterior fontanelle. A ventriculoperitoneal shunt was placed the following day without complications. Ten days after surgery, clear liquid was noted to be leaking from the suture sites on the infant's scalp, and head ultrasonography was performed, which showed stable or slightly decreased ventriculomegaly. Laboratory studies for investigating suspected sepsis (complete blood cell count and C-reactive protein) were found to be reassuring. A shunt tap performed by the neurosurgical team showed that the shunt was functioning appropriately, and CSF studies were found to

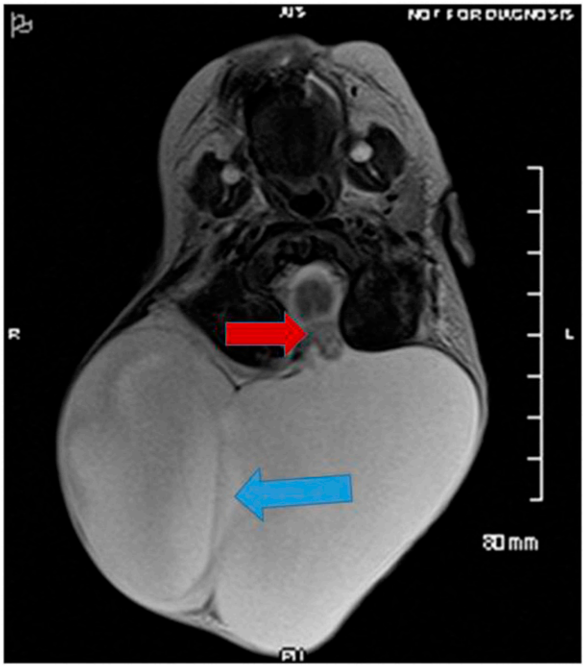

Figure 4. T2-weighted brain magnetic resonance imaging scan.

be similar to prior CSF studies obtained during ventriculoperitoneal shunt placement. After the tap, no further leakage occurred from the surgical site, which continued to heal. CSF culture remained sterile. Oral feedings were started on day 16 of age, and the infant tolerated advancement of feedings. The infant underwent surgical correction of the encephalocele without complication at 1 month of age. The infant continued to take all feedings by mouth and was discharged from the NICU.

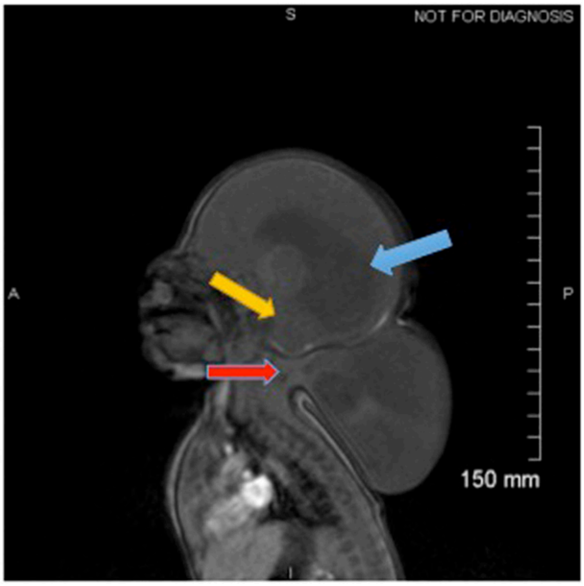

Figure 5. T1-weighted brain magnetic resonance imaging scan.

WHAT THE EXPERTS SAY

An encephalocele results when the anterior neural tube fails to close during development, which results in protrusion of brain and meninges through a bony defect of the skull. This occurs between days 25 to 27 after conception. The occurrence of an encephalocele is reported to be 1 per 5,000 live births. (1) Occipital encephaloceles are the most common type of encephalocele in North America whereas anterior encephaloceles are more common in Southeast Asia. Prognosis is dependent on the amount of herniated brain tissue and on the presence of associated anomalies. Occipital encephaloceles are associated with hydrocephalus and Chiari malformations. (2)(3) Meckel-Gruber syndrome is associated with an occipital encephalocele, postaxial polydactyly, and polycystic dysplastic kidneys. (4) Encephaloceles are also described with schizencephaly and 22q 13 deletion. (5) In our case, an encephalocele was not associated with any abnormality on a microarray analysis. Prenatal imaging can reveal morphologic heterogeneity. In 1 study, Chiari III malformation was seen in almost 50% of cases. (6)

Chiari malformations are defined as structural defects of the cerebellum involving herniation of the cerebellum through the foramen magnum. Four types have been defined.

- Chiari malformation type I occurs when abnormally shaped cerebellar tonsils herniate into the foramen magnum.
- Chiari malformation type II, the classic Arnold-Chiari syndrome, consists of herniation of the cerebellar vermis and tonsils, and a myelomeningocele is usually present.
- Chiari malformation type III (our patient's diagnosis) occurs with an occipito-cervical encephalocele and is associated with prolapse of the lower brainstem into the cervical spinal canal and herniation of cerebellar/dysplastic tissue into the defect. A small posterior cranial fossa, caudally displaced cerebellar tonsils, and hydrocephalus can be seen. Mid-brain abnormalities, such as beaking of the quadrigeminal plate, partial or complete agenesis of the corpus callosum and septum pellucidum, and stenosis or atresia of the cerebral aqueduct are also observed. (7)(8)(9) MRI is the preferred method for diagnosis and description of concomitant brain anomalies.
- Lastly, on the most severe end of the spectrum, Chiari malformation type IV consists of cerebellar hypoplasia and is the rarest of the Chiari malformations.

The treatment for Chiari III malformation is surgical resection to prevent rupture and infection. Shunt placement for managing associated hydrocephalus is usually performed after the primary closure. A few cases of shunt placement before correction of the encephalocele have been reported. (7)(10) Meningitis is described as a common morbidity of surgical interventions. The prognosis for Chiari III malformation is poor. Many infants do not survive the perinatal period because of respiratory failure. Survivors experience neurodevelopmental dysfunction, including respiratory insufficiency, swallowing difficulties and aspiration, cranial nerve palsy, hypo- or hypertonia, bladder and bowel incontinence, seizure disorders, and varying degrees of developmental delay. (10) Some case reports of children with grossly normal motor function or the ability to walk with braces, as well as near-normal language skills, have been documented. (10)(11) Rehabilitation should be individualized to maximize outcomes.

Over half of neural tube defects can be prevented by 400 μg of folic acid daily. (12) It should be noted that neural tube defects caused by primary neurulation defects result in anencephaly and spina bifida; those caused by secondary neurulation defects result in spinal dysraphism with lipoma; and those associated with postneurulation defects result in encephalocele. (13) It is recommended that all women who may become pregnant consume a diet containing adequate folic acid 2 to 3 months before becoming pregnant and throughout the first trimester of pregnancy. For those families who have had a child with a neural tube defect, the recurrence risk is 2% to 3%. This risk can be reduced by approximately 70% with a daily intake of 4,000 μg of folic acid. (12)

The diagnosis of a hemangioma in this case is unlikely because blood would not have been transilluminated. Likewise, the diagnosis of a lipoma is unlikely because adipose cells are not conducive to transmitting light through the skin as a fluid-containing structure would be. In contrast, a diagnosis of cystic hygroma, epidermoid or dermoid cyst, or a teratoma with a significant cystic component would have been transilluminant. However, the head imaging in this case was consistent with an encephalocele and associated Chiari III malformation findings.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the embryology, prevention, incidence, and differential diagnosis of myelomeningocele and encephalocele.
- Know the clinical and imaging findings, treatment, and outcome of myelomeningocele and encephalocele.

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ANSWER KEY FOR FEBRUARY 2020 NEOREVIEWS

Hyperglycemia in Extremely Preterm Infants: 1. D; 2. C; 3. B; 4. E; 5. B.

Iron Nutrition, Erythrocytes & Erythropoietin in the NICU: 1. D; 2. A; 3. A; 4. D; 5. B.

A Newborn with a Large Posterior Head Mass

Whitney D. Ficker, Linda Dunscombe, Naomi Lauriello and Akshaya J. Vachharajani

NeoReviews 2020;21;e145
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Answer Key appears on page e216.

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The Flipped Classroom in Graduate Medical Education

Heather French, MD, MSEd,* AnnaMarie Arias-Shah, MD,† Carly Gisondo, DO,‡ Megan M. Gray, MD§

*Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
†Division of Neonatology, Department of Pediatrics, Baylor College of Medicine, Houston, TX
‡Division of Neonatology, Department of Pediatrics, University of Michigan, Ann Arbor, MI
§Division of Neonatology, University of Washington School of Medicine, Seattle, WA

Abstract

Andragogy, the art and science of helping adults learn, is a learner-centric conceptual framework that considers adult learner characteristics and their motivations for learning. These motivations range from internal will, readiness to learn, and relevance to one's own life. The flipped classroom, an increasingly popular educational method for both learners and educators, aligns with an andragogical approach as it uses classroom time for application of knowledge and critical thinking rather than for a passive didactic lecture. The growing body of educational research demonstrating increased performance and knowledge retention using this method has led to its incorporation into graduate medical education materials, including the National Neonatology Curriculum. In this article, the authors review how the flipped classroom, an active educational method that embraces the tenets of adult learning theory, may be more effective in graduate medical education compared with traditional lecture.

Objectives After completing this article, readers should be able to:

1. Recognize the different learning needs and preferences of adult learners.
2. Explain the benefits of active educational methods, such as the flipped classroom, for adult learners.
3. Describe the educational research supporting the development of the National Neonatology Curriculum.

AUTHOR DISCLOSURE Drs French, Arias-Shah, Gisondo, and Gray have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ABP	American Board of Pediatrics
FC	flipped classroom
GME	graduate medical education
NNC	National Neonatology Curriculum
NNCC	National Neonatology Curriculum Committee
NPM	neonatal-perinatal medicine
ONTPD	Organization of Neonatal-Perinatal Medicine Training Program Directors
PD	program director
RCT	randomized controlled trial

AN INTRODUCTION TO ADULT LEARNING THEORY

Pedagogy, the art and science of teaching children, is a teacher-centric educational approach in which the teacher has full responsibility for decision-making and the learning environment. Pedagogical approaches to education are the predominant form of instruction in higher education in the United States for both children and

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adults. Pedagogy places the student in a submissive role, actively promoting dependence on the instructor. As adults mature, they are increasingly motivated by a desire to solve problems and be self-directed. The pedagogical model does not consider the different developmental needs of adults, which can lead to tension, resentment, and resistance to learning.

Malcolm Knowles, a professor of adult education at Boston University, introduced the idea of andragogy, the art and science of helping adults learn. (1) Andragogy is a learner-centric conceptual framework consisting of 6 assumptions of adult learner characteristics and their motivations for learning (Fig 1). The 6 assumptions that underlie andragogy are: 1) adults are internally motivated and 2) self-directed, choosing what they want to learn, when they want to learn, and how they want to learn; 3) adults bring personal experience to learning; 4) their readiness to learn depends on their need for knowledge; 5) relevance of information for one's personal or professional life; and 6) the usefulness of the information to solve problems. These assumptions of andragogy highlight the differences between child and adult learning in 3 areas: context, learner, and learning processes (Table). (2)(3) Effective educational methods will consider the differences between child and adult learning needs and respect the adult's autonomy.

Pedagogy and andragogy represent the 2 ends of a learning continuum and the use of both teaching approaches may be appropriate for specific topics, regardless of the learner's age. (1) A skilled educator will know when direct instruction, or a pedagogical approach, is best for learners, such as the introduction of new concepts to novice learners, as opposed to when an andragogical approach is best, such as in applying known concepts to complex problems. Capitalizing on an individual's preexisting knowledge allows educators to become facilitators of learning for independent and self-directed learners, rather than transmitters and evaluators of knowledge. (4) Thus, the selection of the educational method is very important for learners to more effectively acquire and retain knowledge. The modified cone of learning (Fig 2), based on research by Edgar Dale, (5) shows the progression of learning experiences from passive to active and suggests that students are capable of retaining 90% of what they learn if educational materials are delivered using active teaching methods.

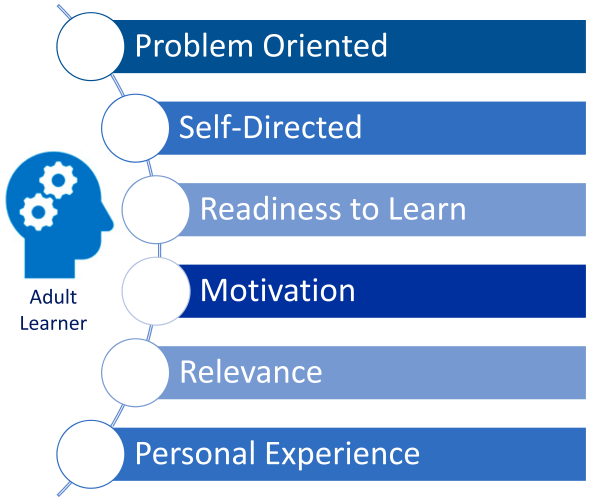

Figure 1. Knowles' assumptions of adult learners.

Effective educational practices in graduate medical education (GME) must consider the following: the learner is an active contributor in the learning process; learning occurs both independently and in collaboration with others in the learning community; preexisting knowledge and past experience provides a framework for acquisition of new knowledge; learning should relate to the understanding and management of real-life problems; placing new knowledge into real-world context enhances learning; and the ability to reflect on knowledge application is critical to the development of lifelong learning skills. Medical educators need to shift learning activities toward approaches that promote higher-level thinking, active learning, and application of learned concepts for highly motivated adult learners. The Accreditation Council for Graduate Medical Education "emphasizes the value of enhancing the quality and quantity of formal teaching, a challenging task due to increasing time constraints for both trainees and faculty members."(6) New strategies, including the "flipped classroom" (FC), have been used in a growing number of medical educational settings.

THE FLIPPED CLASSROOM

The FC approach to education "flips" the traditional classroom approach on its head. (7) Instead of a didactic lecture for knowledge acquisition followed by independent assignments/homework, the learner performs independent, self-paced didactic learning for knowledge acquisition followed by classroom-based group assignments, discussion, and/or problem-based learning. (7) Learner-centric group discussions or problem-based learning facilitated by an educator helps create a community of learning and allows for peer-to-peer teaching, dialogue, and support.

In a traditional didactic classroom, the majority of classroom-based time is spent in the bottom 2 levels of Bloom's taxonomy: remember and understand. (8) In the FC approach, classroom-based time is spent in the higher levels of Bloom's taxonomy: apply, analyze, and evaluate (Fig 3). In the FC approach, adult learners are able to apply knowledge gained through independent study to cases or other

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TABLE. Differences Between Child and Adult Learning

	CHILDREN	ADULTS
Context	• Dependent on others • Learning is main job • Need generalized skills	• Independent of others • Learning is one of many jobs • Need situation-specific skills
Learner	• Requires direction • External motivation • Application to general problems	• Self-directed • Internal motivation • Application to relevant problems
Learning process	• Pace of learning dependent on teacher • Tasks are not always obviously meaningful • External motivation required to learn	• Pace of learning dependent on competing demands • Tasks must be meaningful • Internal motivation required to learn

problem-based discussions during instructor-facilitated, learner-centered activities. (9) These adult learner–centric classroom sessions improve understanding and increase clinical application of acquired knowledge in addition to gaining critical lifelong learning skills. (10)(11)

Educators who participate in FC sessions develop skills as facilitators of learning rather than simply being teachers who transmit knowledge didactically. The interactive nature of the discussions provides the educator with insight into the learners' baseline understanding of the material and provides an opportunity to correct cognitive errors. Depending on the learners' understanding of the material gained in independent study, the facilitator has the ability to target the classroom sessions to the learners' needs, moving the classroom session up or down Bloom's taxonomy.

This approach to education is in alignment with andragogic methodology in its commitment to self-direction, relevance, and orientation to problem-based learning. (12) The FC approach allows adult learners to engage in knowledge acquisition when they are internally motivated, or as needed, based on the relevance of the information to solve clinical problems. The FC allows the learner to participate in knowledge acquisition when it is most convenient for the individual based on internal motivation, clinical schedules, and personal or professional time constraints. The self-directed learner can review assigned materials as many times as necessary to fully understand a concept.

Although there are many benefits of learning in an FC, transitioning to an FC model can be challenging for both learners and educators. The FC is most effective when learners have completed their prework and are prepared to participate actively in classroom-based discussions. This differs from the traditional didactic model where learners are dependent on educators for knowledge acquisition and class preparation is rarely necessary. Ensuring that busy learners are prepared for class can be challenging and requires learners to have internal motivation.

Effective FCs require educators to create a safe learning environment where learners can ask questions of their

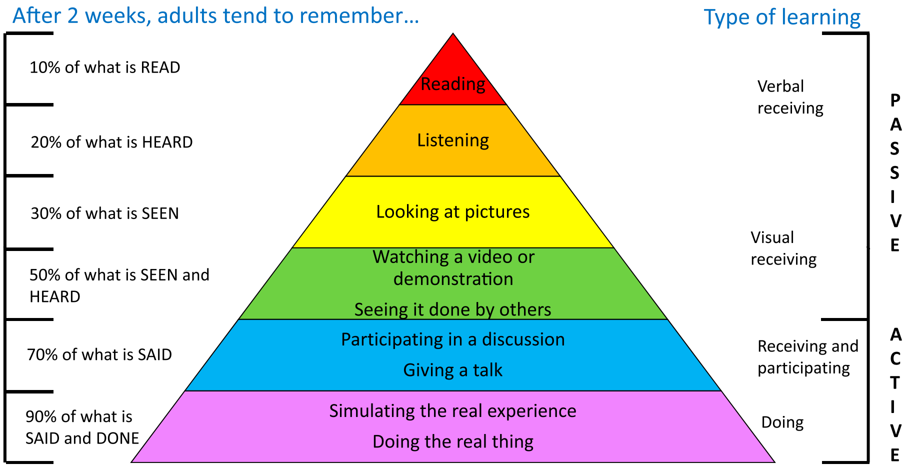

Figure 2. Modified cone of learning based on the original research by Edgar Dale. [5]

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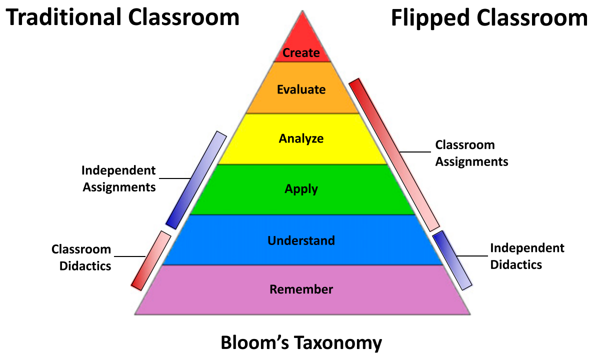

Figure 3. Learning in traditional vs flipped classroom and Bloom's taxonomy.

peers and the educator to clarify concepts. Thus, educator preparation is equally important. Because of the more free-form structure of class time, questions can be asked that expose holes in the educator's knowledge. The educator must be prepared to participate in information gathering during class alongside the learners. Educators must also be prepared to adopt new educational modalities and teaching styles. In the FC, an educator becomes a facilitator of group discussion and asks probing and open-ended questions that promote critical thinking and application of knowledge gained from independent knowledge acquisition. For this to be successful, educators act as a "guide on the side" instead of the traditional "sage on the stage." Making this transition to a new teaching approach can be difficult for some educators.

Converting educational materials into an FC model can be time intensive for educators, depending on the availability of prework activities. Prework activities can include assigned reading, videos, and podcasts. Classroom-based activities need to challenge learners but not be so difficult as to require significant educator explanation. Educator awareness of the learner's fund of knowledge is necessary to plan classroom exercises that reinforce existing knowledge and encourage application of that knowledge in new environments and situations. To encourage collaborative discussion with broad participation, rearrangement of the classroom setup from rows of chairs into a horseshoe or circular setup is beneficial.

Educational Research and Analysis of FCs

The existing research associated with the FC approach has shown growth in both quantity and quality in recent years. A systematic review by Chen et al (9) demonstrated how initial studies on FC efficacy were broad and focused more on evaluating qualitative outcomes. The authors reviewed 9 controlled studies, 8 of which included medical students and 1 involved interns, and concluded that students preferred the FC training method over traditional didactics. (9) However, effects on learning were inconsistent and more studies were deemed necessary. No studies involved subspecialty fellowship learners.

The past few years have shown a rapid increase in research using the FC approach for GME. The growing body of literature suggests popularity of this method among trainees and wide consensus from educators that more rigorous research is needed to determine whether there is evidence for or against the use of FC in medical education. Specifically, studies have shifted from outcomes relating to learner satisfaction or descriptive data to evaluation of knowledge and performance. The metric often evaluated for improved knowledge and performance is immediate posttest scores. Residents in emergency medicine (13) and internal medicine (14) had improved immediate posttest scores with the FC approach. Though promising, the next question posed by educators was whether these effects were sustained. Studies involving residents in internal medicine (14) and anesthesiology (15) demonstrated that improved knowledge acquisition was sustained after several months. Furthermore, one study demonstrated that application of the FC approach to an anatomy course resulted in higher performance both in anatomy and in a subsequent kinesiology course, demonstrating long-term retention and transfer of critical thinking skills to subsequent courses. (16)

Physiology education is an area of study that can benefit from spending class time on clinical application rather than a traditional lecture. FC was shown to be highly effective for reinforcing concepts in cardiovascular, respiratory, and renal physiology as medical students scored significantly higher on standardized examinations. (17) An FC physiology curriculum applied to neonatal-perinatal medicine (NPM) fellowship programs was preferred by both fellows and educators over traditional physiology lectures. Faculty who participated in those FCs found the educational experience to be an effective, useful, and efficient method to apply learning in a supportive environment. (10)

There still remain some mixed results about improved long-term outcomes with use of the FC approach. However, some authors argue that discrepancies in outcomes could be more of a reflection of assessment questions being poorly calibrated to test at high cognitive levels based on Bloom's level of cognition. (18) Regardless, the literature consistently suggests that learners and educators prefer FC methods over traditional didactics. Such findings at least warrant a reevaluation of educational methods for GME curricula and whether they facilitate andragogy.

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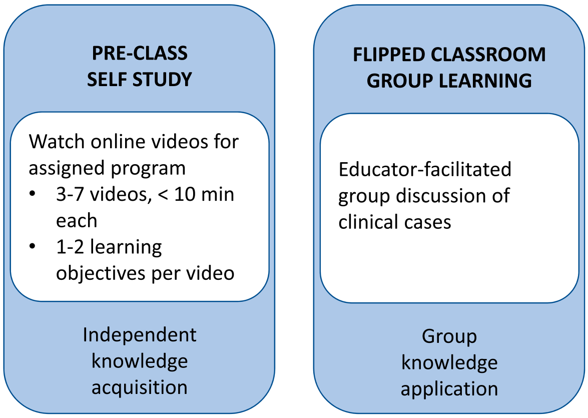
PRE-CLASS
SELF STUDY
Watch online videos for assigned program
3-7 videos, < 10 min each
1-2 learning objectives per video
Independent knowledge acquisition
FLIPPED CLASSROOM
GROUP LEARNING
Educator-facilitated group discussion of clinical cases
Group knowledge application

Figure 4. The National Neonatology Curriculum (NNC) flipped classroom approach.

The National Neonatology Curriculum

In 2016, the Organization of Neonatal-Perinatal Medicine Training Program Directors (ONTPD), NPM fellowship program directors (PDs) and associate PDs reviewed their shared concerns about the development, maintenance, implementation, and effectiveness of educational materials. The group created the ONTPD National Neonatology Curriculum Committee (NNCC) to standardize educational materials with a high-quality physiology curriculum that provided accessible, evidence-based teaching for all NPM fellowship training programs using an FC model. As a first step, the NNCC surveyed PDs and associate PDs nationally to determine their interest in FC education, perceived barriers to FC for neonatology education, and to confirm that physiology was an appropriate initial target for piloting the FC approach. In addition to enthusiasm for the FC project, this survey identified a significant need for educational modalities to address gaps in the quality of fellow education, demands on faculty time, and learner and educator engagement in the learning community.

The NNCC uses high-quality, peer-reviewed educational materials in the form of online videos for independent knowledge acquisition paired with the FC approach for knowledge application. Using the American Board of Pediatrics (ABP) content specifications outline for NPM, programs covering different physiology topics (ie, respiratory distress syndrome, pulmonary function testing) were created by a content expert (neonatologist, perinatologist, or another pediatric subspecialist) and subsequently peer-reviewed/edited by 3 to 4 academic faculty from across the United States. Each program contains 3 to 7 online videos that are short (<10 minutes in duration) and cover 1 to 2 learning objectives each (Fig 4). These online videos are accessible on both desktop and mobile platforms at www.MedEdOnTheGo.com using the search term "Neo Flip." This educational delivery system allows learners to acquire knowledge at the place and time that best suits their learning needs. The videos can be watched multiple times to allow for thorough knowledge acquisition at an individual pace. Each program is paired with a "flipped classroom guide" for interactive classroom discussion and clinical problem solving facilitated by a faculty educator. The FC guide is case-based to place educational content into a clinical context. The guide can easily be individualized based on local or institutional practice and the complexity can be scaled to meet the needs of individual learners.

To date, programs covering respiratory and gastroenterology/bilirubin physiology topics have been completed. Programs in maternal-fetal medicine, neurology, and neurodevelopment are under development. The NNCC has a goal to complete the development of all topics covered by the ABP content outline in NPM within the next 5 years. In addition, an extracorporeal membrane oxygenation course will soon be available. An NPM simulation curriculum is

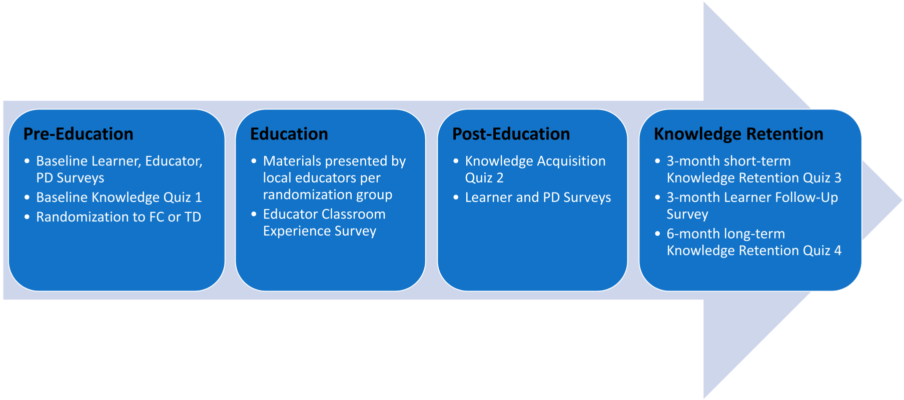
Pre-Education
Baseline Learner, Educator, PD Surveys
Baseline Knowledge Quiz 1
Randomization to FC or TD
Education
Materials presented by local educators per randomization group
Educator Classroom Experience Survey
Post-Education
Knowledge Acquisition Quiz 2
Learner and PD Surveys
Knowledge Retention
3-month short-term Knowledge Retention Quiz 3
3-month Learner Follow-Up Survey
6-month long-term Knowledge Retention Quiz 4

Figure 5. NNC Randomized Controlled Trial Timeline. PD=program director; FC=flipped classroom; TD=traditional didactic.

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also under development, and many simulation exercises will help reinforce key physiologic concepts.

The ONTPD NNC Randomized Controlled Trial

The ONTPD NNCC is committed to rigorous educational research to determine the best approach to fellowship education on a national level. Following a successful pilot (10) and roll-out of the respiratory physiology section (11) of the NNC, a randomized controlled trial (RCT) was launched to study the FC approach for NPM fellow physiology education. The NNC RCT aims to compare knowledge acquisition and retention of fellows taught neonatal gastroenterology and bilirubin ABP NPM board content via the FC approach with those taught using a traditional slide-based didactic approach.

To ensure that the trial could answer important questions about the impact of the FC model, the educational content was standardized across groups but delivery of the material varied. Knowledge acquisition, a primary goal for fellows attending physiology teaching, is being measured via multiple choice questions directly mapped to the learning objectives of the curriculum. Although performance on multiple choice tests does not provide a full picture of an individual's knowledge about a topic, it does closely align with an important performance metric for fellows: performance on the subspecialty in-service and board examinations. (19) Measuring test performance before and right after a series of educational conferences allows for timely collection of other measures of curriculum performance (Fig 5).

NPM learners, educators, and fellowship PDs all provided information on their educational practices and preferences before and after the NNC trial content was taught. Baseline usage of different education modes and ratings of fellowship education will allow for cross-sectional analysis of the variation in educational practices across NPM fellowships. An assessment of barriers to teaching core topics, measures of time investment, and the relative importance of different qualities of the educational environment will provide important information to understand how a national curriculum can best address the needs of both adult learners and educators.

All knowledge degrades with time but learning theory holds that knowledge more deeply understood at the time of acquisition will degrade at a slower rate. (12) To evaluate whether the initial educational modality affects knowledge retention and degradation, the NNC RCT includes follow-up knowledge assessments 3 and 6 months after the educational intervention. Understanding the pattern of knowledge retention in fellow level learners will further help to inform educational programs that support the mission of developing neonatologists with a deep understanding of physiology and the skills to remain lifelong learners.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand the basic principles of adult learning theory (eg, adult learners are self-directed, goal-oriented, practical; need to feel respected, build on life experiences; learn best when learning is based on an existing framework).
- Understand the attributes of an effective learning environment.
- Understand the importance of "reflective practice" in teaching and learning.
- Identify strategies that motivate learners.
- Understand the strengths and weaknesses of various teaching methods (eg, lecture, small group discussion, bedside teaching, simulation).
- Understand that individuals may learn more effectively with certain teaching methods (eg, reading, hearing, doing) than with others.
- Recognize the strengths and weaknesses of various educational outcome measures (eg, participant satisfaction, acquisition of knowledge and skills, behavioral change, patient outcomes).
- Understand the role of needs assessment in educational planning.

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Inhaled Nitric Oxide in Emergency Medical Transport of the Newborn

Jason Gien, MD,*† Craig Nuxoll, RRT,† John P. Kinsella, MD*†

*Section of Neonatology, University of Colorado School of Medicine, Aurora, CO
†Children's Hospital Colorado, Aurora, CO

Education Gaps

Randomized controlled trials have shown that inhaled nitric oxide is safe and effective to treat near-term and term newborns with hypoxemic respiratory failure and pulmonary hypertension. However, continued use of inhaled nitric oxide use during transport of a sick newborn to a facility that offers the potential for extracorporeal membrane oxygenation is challenging. This review will provide the reader with a practical approach to the use of inhaled nitric oxide before and during transport.

Abstract

Randomized controlled trials in the 1990s confirmed the safety and efficacy of inhaled nitric oxide (iNO) in near-term and term newborns with hypoxemic respiratory failure and pulmonary hypertension, demonstrating improved oxygenation and reduced need for extracorporeal membrane oxygenation (ECMO) therapy. However, in about 30% to 40% of sick newborns, these improvements in oxygenation and hemodynamics are not sustained and affected infants often require rapid transfer to an ECMO center despite the initiation of iNO. Abrupt discontinuation of iNO therapy before transport in patients who have had little apparent clinical benefit can be harmful because of acute deterioration with severe hypoxemia. Thus, continued use of iNO therapy during hospital transfer of infants with pulmonary hypertension is important. In this review, we describe: 1) the history of iNO use during transport; 2) a practical approach to iNO during transport; and 3) guidelines for the initiation of iNO before or during transport.

Objectives

After completing this article, readers should be able to:

1. Explain the history and evolution of inhaled nitric oxide (iNO) use in transport
2. Describe a practical approach to iNO use during transport
3. Provide a summary of guidelines for iNO use during transport

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ABBREVIATIONS

CDH	congenital diaphragmatic hernia
ECMO	extracorporeal membrane oxygenation
FDA	Food and Drug Administration
HFOV	high-frequency oscillatory ventilation
iNO	inhaled nitric oxide
NO	nitric oxide
NO_2	nitrogen dioxide
PPHN	persistent pulmonary hypertension of the newborn

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INHALED NITRIC OXIDE DURING TRANSPORT

Randomized controlled trials in the 1990s confirmed the safety and efficacy of inhaled nitric oxide (iNO) in near-term and term newborns with hypoxemic respiratory failure and pulmonary hypertension, demonstrating improved oxygenation and reduced need for extracorporeal membrane oxygenation (ECMO) therapy. (1)(2)(3)(4) However, in about 30% to 40% of sick newborns, these improvements in oxygenation and hemodynamics are not sustained and affected infants often require rapid transfer to an ECMO center despite the initiation of iNO. Abrupt discontinuation of iNO therapy before transport in patients who have had little apparent clinical benefit can be harmful because of acute deterioration with severe hypoxemia. (5)(6)(7) Indeed, an early report described a death associated with the discontinuation of iNO before transport to an ECMO center. (8) Thus, continued use of iNO therapy during hospital transfer of infants with pulmonary hypertension is important. In this review, we describe: 1) the history of iNO use during transport; 2) a practical approach to iNO during transport; and 3) guidelines for the initiation of iNO before or during transport.

HISTORY OF iNO USE DURING TRANSPORT

The use of iNO in infants was approved by the United States Food and Drug Administration (FDA) in 1999. Emergency transport using iNO was offered as early as 1993 in a select group of infants who were considered extremely unstable for transport based on the severity and lability of their cardiopulmonary disease. (5) The successful transport of 6 patients with hypoxemic respiratory failure and pulmonary hypertension who were treated with iNO was first reported in 1995. Infants varied in age from less than 15 days to 7.5 months and had severe hypoxemia with marked lability despite receiving aggressive treatment with mechanical ventilation and fraction of inspired oxygen of 1.00 at the referring hospital. (5) Initiation of iNO caused marked improvements in oxygenation that was sustained for the duration of the transport.

In 1996, Tang and Miller described the successful transport of 3 newborns with meconium aspiration syndrome and persistent pulmonary hypertension of the newborn (PPHN) using conventional mechanical ventilation and iNO for stabilization; these infants were transported from a small regional NICU to a center with a higher level of neonatal intensive care that could provide continuous nitric oxide (NO), high-frequency ventilation, and ECMO. (9) In 2002, Kinsella et al published their experience with 25 term newborns who were transported while receiving iNO therapy. (10) The authors described the successful transfer of 10 infants with congenital diaphragmatic hernia (CDH), 6 infants with PPHN, 4 infants with meconium aspiration syndrome, 4 infants with sepsis, and 1 infant with non-CDH pulmonary hypoplasia to a higher acuity center capable of providing ECMO therapy. (10) Infants were 3 days old at the time of transport and the average duration of transport was less than 2 hours. All patients had severe hypoxemia before transport as assessed by the alveolar-arterial ratio. In 3 cases, iNO therapy was initiated by the referring center and continued during transport. In the remainder of cases, treatment with iNO was initiated by the transport team for severe hypoxemia refractory to conventional therapy. In 15 patients, iNO was initiated at the referring hospital to stabilize the infant's oxygenation and allow the infant to be transitioned from high-frequency oscillatory ventilation (HFOV) (Sensormedics$^{\text{TM}}$ 3100A, Vyaire Medical, Mettawa, IL) to conventional mechanical ventilation. Half of the patients were transported by ground ambulance and the remainder by fixed-wing aircraft. Oxygenation improved after initiation of iNO therapy at the referring hospital, and this improvement was sustained, with all patients surviving transport. (10) Since then, iNO has been used routinely to transport critically ill newborns to centers capable of providing advanced therapies such as ECMO.

Transport with iNO has also been described in adults. Teman et al described the initiation of iNO in 139 patients (median age of 45 years) with cardiopulmonary failure in anticipation of transfer to a tertiary care center. iNO was started by the transport team in 114 patients and initiated at the referring hospital in 25 patients. (11) The authors found that all patients who received iNO had significant improvement in their oxygenation. Those patients who continued to receive iNO (n=102) had no complications during transport. iNO was discontinued in 35 nonresponders, and of these, 15 could not be transferred because of life-threatening hypoxemia; 2 of the 15 patients were later transferred while receiving ECMO. (11)

In the event of a suboptimal response to iNO, non-ECMO centers that offer iNO therapy to infants should have an iNO transport system available and be prepared to initiate early referral. In the largest published report in infants receiving iNO during transport, (12) Lowe and Trautwein sought to determine whether initiating iNO before transport of critically ill neonates with severe hypoxemic respiratory failure and/or PPHN would decrease the need for ECMO, reduce the number of hospital days, and improve survival compared with initiating iNO after the infant was transported to the receiving hospital. (12) Although earlier initiation of iNO

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did not decrease the need for ECMO or improve survival, initiating iNO at the referring hospital was associated with decreased length of hospitalization in those infants not requiring ECMO.

DELIVERY OF iNO DURING TRANSPORT

Between 2015 and 2017, iNO was used for 51 infants during transport to our NICU at Children's Hospital Colorado. For the majority of patients (40/51 [78%]), iNO was initiated at the referring hospital and the infant was receiving iNO at the time of transport request. This is similar to the report described previously, in which 70% of patients were treated with iNO before the transport was requested. (12) For the remaining infants (11/51 [22%]), iNO was initiated by the transport team on arrival at the referring hospital. Diagnoses included PPHN (n=22), bronchopulmonary dysplasia (n=2), meconium aspiration (n=6), pulmonary hemorrhage (n=2), pulmonary hypoplasia (n=1), CDH (n=3), omphalocele (n=1), tracheoesophageal fistula (n=1), transposition of the great vessels (n=2), bowel perforation (n=2), sepsis with respiratory failure (n=7), bronchiolitis (n=1), and hydrops (n=1). Transport trips varied in distance, with 14 (27%) of 51 patients transported by ground, 17 (33%) transported by rotary-wing aircraft (ie, helicopter), and 20 (39%) by fixed-wing aircraft. The majority of infants (38/51 [75%]) were of term gestational age. Most infants (30/51 [59%]) were transported with high-frequency ventilation using the TXP-2D™ high-frequency transport ventilator (Percussionaire, Sandpoint, ID) with iNO delivery via the Phasitron interface (Percussionaire).

There are several challenges in transporting infants with iNO using high-frequency ventilation. Two devices are currently available for infant transport with high-frequency ventilation (1): the TXP-2D high-frequency transport ventilator, and (2) the Bronchotron high-frequency ventilator (Percussionaire). Delivering an accurate amount of iNO is challenging during transport, particularly when high-frequency ventilation is needed. One option for delivering iNO is to use the iNO injector module with the INOmaxDSIR™ delivery system (Mallinckrodt Pharmaceuticals, St Louis, MO). This system uses a mass flow controller to determine the gas flow rate in the ventilator circuit and then delivers the proper flow of source NO gas to produce a constant iNO delivery rate in parts per million.

Branson et al compared iNO delivery with high-frequency ventilation using 4 configurations of the Transport Sinusoidal Bronchotron, Phasitron, injector module, and the DSIR iNO delivery system. (13) When the injector module was placed between the Bronchotron and the Phasitron (Fig, A) the additional compressible volume caused a decrease in the pressure amplitude to 25% of the initial setting (10 cm H_2O) and the positive end-expiratory pressure to half of the initial setting. In this study, the failure of this configuration to reproduce the ventilator settings led to abandonment of this approach. When the delivery system B and C shown in the Figure was used, there were differences between the set and the delivered iNO amount of 65% to 83%. When the injector module was placed in line distal to the Phasitron (Fig, D), there were significant increases in the set versus delivered iNO of 11 to 30 ppm. Moreover, increases in nitrogen dioxide (NO_2) to 2.3 ppm were measured (baseline measurement=0). The authors concluded that, depending on where the injector module is placed, high-frequency percussive ventilation gas delivery prevents accurate delivery of the set ventilator settings or the set iNO concentration.

Before the current study, we used delivery system D shown in the Figure. We found significant increases in set versus delivered iNO of 11 to 30 ppm with this configuration. Using a sample line (ie, tubing that connects to the ventilator circuit and allows for measurements of gas concentrations during exhalation or inhalation) and test lung, we determined that setting the delivered iNO at 5 ppm resulted in 20 ppm being delivered to the patient, without accumulation of toxic NO_2 metabolites. As a result, we investigated other iNO delivery systems. The AeroNOx™ NO delivery system (International Biomedical, Austin, TX) provides a constant concentration of NO by delivering a set flow of 800 ppm into the inspiratory limb of the mechanical ventilator without an injector module piece. Because the Bronchotron high-frequency ventilator is dependent on a flow rate of 15 L/min, depending on the flow setting on the AeroNOx NO delivery system, variable concentrations of iNO will be delivered to the patient. Using the AeroNOx device, flow is adjusted to deliver the desired dose, which is measured by an in-line sample port. AeroNOx was approved by the FDA in 2015; it is currently the only FDA-approved device compatible with high-frequency transport devices and is therefore recommended when using high-frequency ventilation with iNO during transport.

GUIDELINES FOR iNO USE DURING TRANSPORT

When iNO is brought on transport, all of the relevant equipment should be mounted directly on the patient stretcher or isolette. At our center, we use an 800 ppm NO tank, which is firmly secured upright to keep the tank from falling or being knocked over; the cylinder contains

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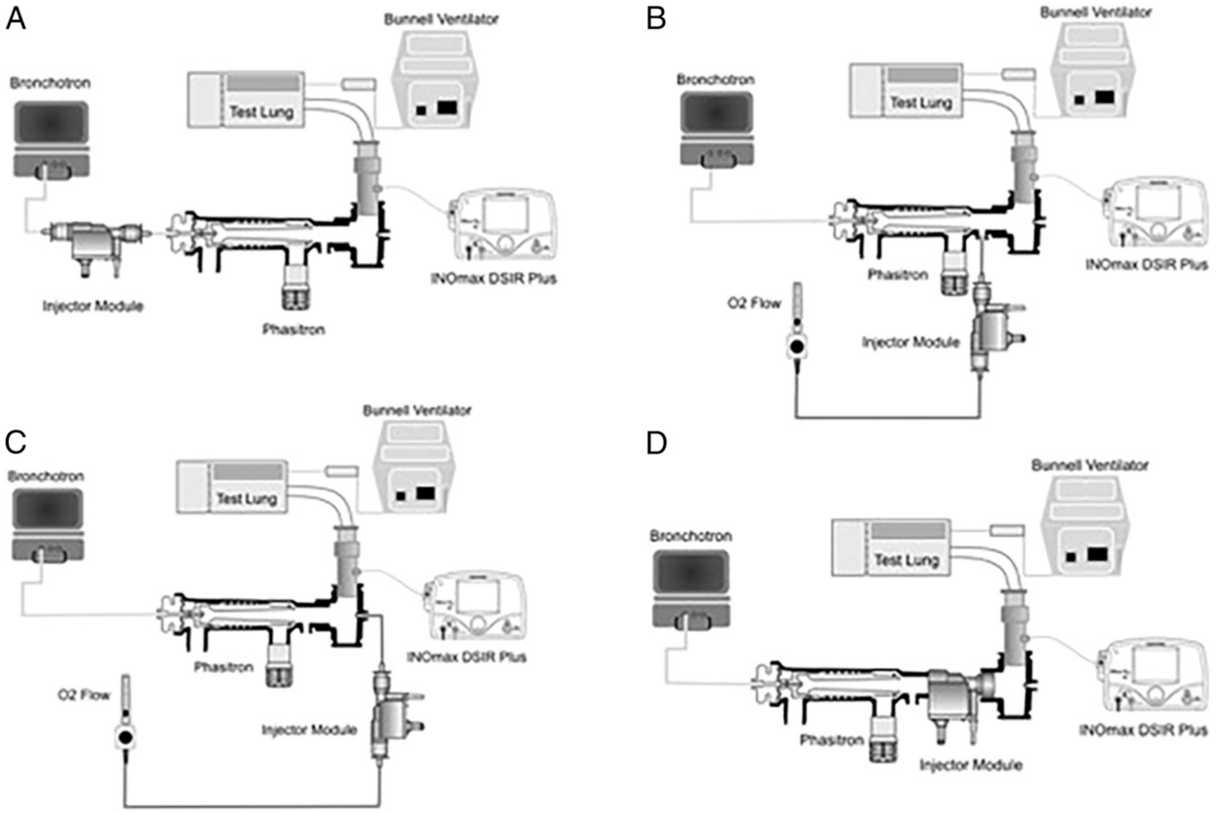

Figure. Different configurations for the delivery of inhaled nitric oxide. Reprinted with permission from Branson RD, Griebel J, Rodriguez D Jr. A bench study of inhaled nitric oxide during high frequency percussive ventilation. *Pediatr Pulmonol.* 2018;53(3):337–341. (13)

compressed gas under high pressure with 2,000 pounds per square inch gauge.

Our current indications for iNO use during newborn transport include patients receiving iNO at the referring hospital, a diagnosis of PPHN in the setting of optimal lung inflation, and the absence of congenital heart disease with ductal-dependent systemic blood flow (Table). Before transport, we place pre- and postductal oxygen saturation probes and obtain a chest radiograph to ensure that lung volumes are adequate. If possible, we recommend obtaining an echocardiogram to rule out structural and functional contraindications (anatomic defects with ductal-dependent systemic blood flow or severely diminished left ventricular performance) to iNO use. Although many neonates with disorders associated with PPHN demonstrate clinical improvement with iNO treatment, some patients do not respond. This clinical variability in iNO responsiveness may be partly because of poor lung inflation that prevents adequate delivery of iNO. (14) For this reason, if an infant's lung volumes are inadequate on chest radiography, we routinely use lung recruitment strategies such as high-frequency ventilation before initiating iNO. For emergency medical transport, we use the TXP high-frequency transport device. Poor iNO responsiveness also may be related to myocardial dysfunction, in particular left ventricular diastolic dysfunction in newborns with CDH (15) and unrecognized anatomic cardiovascular lesions. Because iNO is usually coadministered with high concentrations of oxygen, there is a risk of increased reactive oxygen and reactive nitrogen metabolites, which may induce vasoconstriction and/or inadequate responses to iNO. (16)(17)

iNO can be administered through conventional mechanical ventilation, high-frequency ventilation, or noninvasive devices. For our transport team, the recommended dose of iNO is 20 ppm for term infants. If a patient has been receiving iNO before the transport team's arrival, it is our standard practice to continue the patient's current dose. If iNO is discontinued before transport, the infant should be stable without iNO therapy for at least 1 hour before transport. In the neonate receiving ventilation, the amount of inspired NO and NO_2 should be monitored before transport, if time allows, with a properly calibrated analysis device with alarms. The sample that is analyzed should be drawn before the Y-piece, which is proximal to the patient.

Although severe PPHN is commonly associated with near-term and term neonates, pulmonary hypertension

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TABLE. **Suggested Approach for iNO Therapy during Neonatal Transport**

BEFORE TRANSPORT
Determine mode of ventilation that is needed and available
Determine mode of transportation that is ideal for clinical scenario
Communicate with accepting hospital
Mount equipment directly onto transport isolette; ensure that NO tank is upright and secured
Place pre- and postductal oxygen saturation probes on infant
Adjust ventilator settings to ensure that lung volumes are adequate by chest radiograph
Optimize cardiovascular status
If initiating iNO for transport, use iNO dose of 20 ppm for term infants; for preterm infants, initiate iNO at dose 5 ppm and increase for response in 5 ppm increments to maximum dose of 20 ppm
Measure amount of inspired NO and NO_2 (if time allows)
DURING TRANSPORT
If iNO is started before transport, continue with the same dose during transport
Monitor infant's vital signs
Frequent communication with accepting hospital about infant's clinical status and expectation of whether ECMO might be needed

ECMO=extracorporeal membrane oxygenation; iNO=inhaled nitric oxide; NO=nitric oxide; NO_2=nitrogen dioxide

may complicate the course of preterm newborns, particularly those with pulmonary hypoplasia associated with prolonged rupture of membranes. (18)(19) We have limited the use of iNO in preterm infants to those with PPHN physiology and extrapulmonary right-to-left shunting that persists after optimizing lung inflation, causing severe hypoxemia. We typically start iNO at 5 ppm in preterm infants and increase the dose, based on clinical response, in 5-ppm increments to a maximum of 20 ppm.

MODE OF TRANSPORT

For transport of critically ill newborns, the mode of transport (ie, ground ambulance, rotary-wing aircraft, fixed-wing aircraft) depends on the urgency, weather conditions, and distance to the referring hospital. Ambulance ground transportation can be used in any weather condition but because of speed limitations, ground transportation is generally not used for distances of more than 50 miles, unless weather conditions prohibit use of other modes. Helicopters have several benefits, making air transport the mode of choice for longer distances when weather permits. Depending on the helicopter, speeds of 180 miles/hour can be reached, minimizing the out-of-hospital time. Disadvantages to rotary-wing transport include cost; need for a landing zone in close proximity to the hospital; likelihood of grounding because of adverse weather conditions; challenges in adequate patient assessment and/or interventions during flight as a result of high environmental noise and vibration levels; and restricted patient access during flight. Fixed-wing aircraft options include twin engine propeller aircraft and private jet aircraft. Twin engine aircraft can reach 300 miles per hour and have a range of 400 miles before requiring refueling. Private jet aircraft can reach speeds of 500 miles/hour with a range of 1,150 miles before requiring refueling. Other benefits of fixed-wing transport include efficient fuel costs over long distances and more interior space, allowing for good access to the patient during the flight. The obvious disadvantage of fixed-wing transports is the distance to the airport from both the referring and accepting hospitals, increasing the time needed for team ground transfers, and prolonging out of hospital time.

To our knowledge, to date, the Federal Aviation Administration has not developed a uniform policy to guide the use of iNO on fixed-wing or rotary-wing flights and each of the 9 regions within the United States has determined its own policy. In the Rocky Mountain region, requirements for the use of iNO during transport include the following: 1) the aircraft must be approved for use of iNO by the hazardous materials program; 2) it must have appropriate storage of iNO based on the guidelines for the transport of compressed gases; 3) the team must use a safety data sheet; and 4) the pilot must be aware that iNO is aboard the aircraft.

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Kinsella et al studied the effects of iNO delivery systems on ambient NO concentrations in commonly used transport vehicles. (10) They blended NO at a delivered concentration of 40 ppm in a ventilator system using 20 L/min of gas flow. NO and NO_2 concentrations were measured during mock transports in the fixed-wing Learjet^{TM} 35 (Bombardier Inc, Montreal, Canada), King Air^{TM} 90 and 200 aircrafts (Beechcraft, Wichita, KS), A-Star^{TM} 350 helicopter (Airbus, Leiden, Netherlands), and ground ambulance. Measured ambient NO and NO_2 concentrations were less than 1 ppm (ie, 0 ppm using electrochemical detection). The authors also studied a "worst-case scenario" with complete release of a "D" cylinder in the cabin of each vehicle using different cabin volumes and air exchange rates. (10) Complete air exchange refers to how much time it takes to completely exchange out air in the cabin. The Learjet 35 has a cabin volume of 322 cubic feet, the King Air 90 and 200 aircrafts have a cabin volume of 247 and 393 cubic feet, respectively, and the A-Star 350 helicopter has a cabin volume of 106 cubic feet. In the Learjet 35 and the King Air 90 and 200 aircrafts, complete air exchange of the cabin occurs in 1.25, 4.8, and 4.1 minutes, respectively. Because the A-Star 350 helicopter is not pressurized, the air exchange is variable. Without air exchange (ie, instantaneous maximal concentration), the complete release of a D cylinder would yield a maximum concentration of 30.8 ppm NO in the Learjet 35, 40.2 ppm in the King Air 90, and 25.3 ppm in the King Air 200 aircrafts. Because of the nonpressurized small cabin volume in the A-Star 350 helicopter, instantaneous maximum NO concentration after complete release of a D cylinder could reach levels of 94 ppm. Finally, the ground ambulance has a cabin volume of 289 cubic feet and the rate of air exchange is variable. In this vehicle, the estimated maximum concentration of NO would be 34 ppm. To put these data in perspective, acceptable average exposures to NO in the workplace are 25 ppm, with transient exposures ranging up to 100 ppm.

CONCLUSION

Clinical trials have demonstrated acute and sustained improvement in oxygenation with iNO therapy in many newborns with PPHN; however, with abrupt discontinuation, an acute life-threatening deterioration may occur. (14) iNO is widely available and is used in many NICUs that are unable to provide advanced medical therapies such as ECMO. If the response to iNO therapy is suboptimal, non-ECMO centers should have an iNO transport system available to transport the patient to an ECMO center. During transport, continued use of iNO may help to decrease pulmonary vasoreactivity and prevent pulmonary hypertensive episodes; thus, the capability of sustaining iNO delivery during emergency medical transport is important.

Published reports confirm that iNO therapy can be safely used during infant transport. Moreover, measurements in the cabin during the various air transport options show that ambient NO and NO_2 concentrations remain within safe ranges when using iNO during transport. In addition, limited evidence suggests that there may be benefit to early initiation of iNO at the referring hospital before transport. For infants who require emergency medical transport and have not been treated with iNO, before initiation at a non-ECMO center, attention should be given to optimizing cardiovascular stability and lung inflation. When available, careful echocardiographic examination should be performed to rule out structural and functional contraindications to initiation of iNO.

Depending on the region, attention should be paid to the availability of high-frequency ventilation during transport, which creates unique challenges, particularly for iNO delivery. Because the Sensormedics 3100A HFOV has not been configured for use in fixed-wing or helicopter transport and is cumbersome for ground transport, the TXP-2D high-frequency transport ventilator or the Bronchotron high-frequency ventilator are alternate options that can be configured for iNO delivery during transport. In regions where high-frequency ventilation is not available for transport, stabilization with conventional mechanical ventilation strategies should be attempted before transport.

Finally, evidence on the safety and effectiveness of using iNO to stabilize preterm newborns (<34 weeks' gestation) during emergency medical transport is insufficient. Multiple clinical trials suggest that routine use of iNO for the prevention and/or treatment of bronchopulmonary dysplasia is currently not recommended. (20)(21)(22)(23)(24)(25) Therefore, iNO use during the transport of preterm infants should be reserved for infants with echocardiographic evidence of PPHN causing critical hypoxemia.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the management of persistent pulmonary hypertension including assisted ventilation, pharmacologic approaches, and ECMO.

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1. Inhaled nitric oxide (iNO) is effective for the treatment of hypoxemic respiratory failure and pulmonary hypertension in near-term and term newborns. When did the United States Food and Drug Administration (FDA) approve the use of iNO in infants?
   - A. 1980.
   - B. 1985.
   - C. 1992.
   - D. 1999.
   - E. 2005.
2. Although iNO has been shown to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) therapy in neonates with hypoxic respiratory failure and pulmonary hypertension, some neonates do not have a sustained response. What is the percentage of neonates who do not respond to iNO in a sustained manner?
   - A. 5%.
   - B. 10%.
   - C. 15%.
   - D. 20%.
   - E. 30%.
3. The clinical variability in iNO responsiveness is likely multifactorial. Which of the following has NOT been shown to represent a risk factor for iNO nonresponsiveness?
   - A. Poor lung inflation.
   - B. Sepsis.
   - C. Myocardial dysfunction.
   - D. Vasoconstriction due to increased reactive oxygen and reactive nitrogen metabolites.
   - E. Left ventricular diastolic dysfunction in newborns with CDH
4. Neonates with pulmonary hypertension who do not respond to iNO may require a rapid transfer to an ECMO center. Discontinuation of iNO for transport is not recommended because of the possibility of acute decompensation with severe hypoxemia. Which of the following has been associated with earlier initiation of iNO before transport?
   - A. Decreased need for ECMO.
   - B. Improved survival.
   - C. Decreased length of hospitalization in infants not requiring ECMO.
   - D. Decreased mechanical ventilation days.
   - E. Decreased duration of ECMO.
5. Delivering an accurate amount of iNO is challenging during transport, particularly when high-frequency ventilation is needed. The AeroNOx^{TM} nitric oxide delivery system (International Biomedical, Austin, TX) is currently the only FDA-approved device compatible with high-frequency transport devices. Which of the following statements regarding delivery of iNO using this system is INCORRECT?
   - A. Provides a constant concentration of iNO.
   - B. Has a set flow of 400 ppm.
   - C. Delivers NO into the inspiratory limb of the mechanical ventilator.
   - D. Does not use an injector module piece.
   - E. Allows for constant monitoring of the iNO dose via an in-line sample port.

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Milrinone Use in Persistent Pulmonary Hypertension of the Newborn

Amna Qasim, MD,* Sunil K. Jain, MD†

*Department of Pediatrics, Division of Pediatric Cardiology, Texas Children's Hospital/Baylor College of Medicine, Houston, TX
†Department of Pediatrics, Division of Neonatology, University of Texas Medical Branch, Galveston, TX

Practice Gaps

1. Understanding the pathophysiology of persistent pulmonary hypertension of the newborn (PPHN) and its related myocardial dysfunction is important for the appropriate management of affected neonates.
2. The use of inotropes, lusitropes, and vasopressor agents is common in neonates with cardiovascular compromise secondary to PPHN. The clinically relevant long-term benefits of these agents in the neonatal population are still unknown.
3. There is not much evidence on the choice, timing of initiation, dosing, monitoring, and titrating of vasoactive agents in the neonatal population. (1)

Abstract

Failure of the normal transition from in utero to ex utero physiology leads to "*persistent*" pulmonary hypertension of the newborn (PPHN). PPHN is frequently associated with low systemic blood pressure and low cardiac output because of increased right ventricular afterload and myocardial dysfunction. The general management of newborns with PPHN is geared toward maintenance of normothermia, normal serum electrolytes, normal intravascular volume, correction of acidosis, adequate sedation/analgesia, adequate ventilation and oxygenation with optimal lung recruitment, and avoidance of hyperoxia. Inotropic and vasoactive agents are commonly initiated early to increase cardiac output, maintain adequate systemic blood pressure, and enhance oxygen delivery to the tissue. Unfortunately, there is not much evidence on the choice, timing of initiation, dosing, monitoring, and titrating of vasoactive agents in this patient population. In this review, we will discuss the pathophysiology of PPHN and review the use of inotropic, lusitropic, and vasoactive agents in the management of PPHN, with particular attention to milrinone.

AUTHOR DISCLOSURE Drs Qasim and Jain have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
ECMO	extracorporeal membranous oxygenation
eNOS	endothelial nitric oxide synthase
iNO	inhaled nitric oxide
LV	left ventricular
NO	nitric oxide
OI	oxygenation index
PAP	pulmonary arterial pressure
PBF	pulmonary blood flow
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDE	phosphodiesterase
PFO	patent foramen ovale
PPHN	persistent pulmonary hypertension of the newborn
PVR	pulmonary vascular resistance
RV	right ventricular
SaO_2	saturation of arterial oxygen
SAP	systemic arterial pressure
SVR	systemic vascular resistance

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Objectives After completing this article, readers should be able to:

1. Describe the pathophysiology of the fetal circulation and compare the normal versus abnormal cardiopulmonary transition after birth
2. Recognize the role of pulmonary vasodilators in the management of persistent pulmonary hypertension of the newborn (PPHN)
3. Identify the appropriate inotropic or vasoactive agent for hemodynamic compromise of neonates with PPHN.

INTRODUCTION

The transition from the intrauterine to extrauterine environment signifies a critical stage of physiologic adaptation. This can affect many organ systems, most notably the cardiovascular and pulmonary systems. Most neonates complete this physiologic transition without any complications. However, if there is any dysregulation in this postnatal adaptation, the neonate can experience acute cardiopulmonary instability. Failure of the normal physiologic decrease in pulmonary vascular resistance (PVR) leads to persistent pulmonary hypertension of the newborn (PPHN), also known as *persistent fetal circulation*. PPHN is characterized by persistent elevation of the PVR with higher right-sided intracardiac pressures that lead to hypoxemia as a result of extrapulmonary right-to-left shunting of blood across the patent ductus arteriosus (PDA) and patent foramen ovale (PFO). Optimization of the circulatory hemodynamics is crucial for management in neonates with PPHN and requires a thorough understanding of the mechanisms of action of various treatment modalities. In addition, comprehensive hemodynamic monitoring is necessary to improve the ability to accurately identify the underlying pathophysiology.

Possible management strategies of neonates with PPHN include:

- minimizing environmental factors that increase PVR (eg, noxious stimuli, lung overdistention)
- adequate lung recruitment and alveolar ventilation
- hemodynamic assessment and appropriate fluid and cardiovascular resuscitation with inotropic and vasoactive agents
- inhaled nitric oxide and other pulmonary vasodilators such as phosphodiesterase 5 inhibitors (sildenafil), endothelin receptor antagonists (bosentan), or prostacyclines (iloprost)

In this review, we describe the mechanisms of action of the most frequently used cardiovascular medications in infants with PPHN, with particular attention to the role of milrinone in the management of PPHN.

FETAL AND TRANSITIONAL CARDIOPULMONARY CIRCULATION

Fetal Circulation

During the intrauterine period, the fetus has increased pulmonary arterial pressure (PAP), leading to a state of physiologic pulmonary hypertension. PAP is determined by pulmonary blood flow (PBF), PVR, and the pulmonary capillary wedge pressure (PCWP) (2):

$$\text{PAP} = (\text{PBF} \times \text{PVR}) + \text{PCWP}$$

An increase in any of these determinants may lead to an elevated PAP. In the fetal circulation (and in neonates with PPHN), the PVR is the most significant determinant of maintaining an elevated PAP. The intrauterine pulmonary circulation has high PVR, which leads to decreased PBF with less than one-fifth of the combined ventricular cardiac output going to the lungs. Because of elevated intrauterine PVR, most of the right ventricular output bypasses the fetal lungs and enters the descending aorta through the ductus arteriosus, which increases umbilical-placental blood flow and placental gas exchange. (3) Various factors play a role in causing the elevated fetal PVR, including hypoxemia, fluid-filled lungs, decreased levels of nitric oxide and prostacyclin, and increased levels of endothelin-1, leukotrienes, and Rho-kinase. (4)(5)(6)

At Birth

At birth, the removal of the low-resistance placental circulation increases the systemic vascular resistance (SVR). At the same time, the PVR decreases rapidly in the setting of

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increased oxygen exposure, resulting in a significant increase in PBF (8–10 times). This leads to a reversal in blood flow across the ductus arteriosus (left-to-right) as the PVR drops below the SVR and this oxygenated blood flow helps initiate the closure of the ductus. This is soon followed by structural remodeling of the pulmonary vasculature with an additional decrease in the PVR. (7) Several factors contribute to the pulmonary vasodilation that occurs at birth; these include alveolar distention, absorption of fetal lung fluid, increased partial pressure of oxygen, and increased production of nitric oxide (NO). Cornfield et al demonstrated that the increase in NO production accounts for the significant drop (almost half) in PVR at birth in fetal lambs. (8)

The increase in NO at birth is attributable to an increase in the activity of endothelial NO synthase (eNOS) and cyclooxygenase. (5)(8)(9) NO promotes pulmonary vasodilation via the cyclic guanosine monophosphate (cGMP) and the prostacyclin–cyclic adenosine monophosphate (cAMP) pathways. (10) These pathways play a key role in the perinatal circulation (Fig 1). (11)

MALADAPTATION OF CARDIOPULMONARY CIRCULATION AT BIRTH

PPHN is a clinical syndrome characterized by hypoxemia secondary to increased PVR, which leads to persistence of right-to-left extrapulmonary shunting of deoxygenated blood, that is, persistence of the fetal circulation. PPHN may be associated with diverse neonatal cardiopulmonary conditions including:

- *Maladaptation of the pulmonary vasculature,* whereby the pulmonary vasculature is structurally normal but constricted. This can be associated with lung parenchymal diseases such as meconium aspiration syndrome, respiratory distress syndrome, pneumonia, and sepsis
- *Remodeled or maldevelopment of pulmonary vasculature* with normal lung parenchyma; this is also called idiopathic or primary PPHN
- *Hypoplastic or underdevelopment of pulmonary vasculature* as seen in lung hypoplasia secondary to congenital diaphragmatic hernia, severe and prolonged oligohydramnios, and intrauterine growth restriction
- Intravascular obstruction
- Pulmonary venous hypertension (12)(13)

The clinical presentation of PPHN consists of refractory hypoxemia with a gradient in preductal and postductal oxygen saturations (SaO_2). A high index of clinical suspicion is necessary in an infant who develops hypoxemia and respiratory distress in the first 24 hours after birth and has risk factors (eg, asphyxia, meconium aspiration syndrome, respiratory distress syndrome, post-term gestation of >41 weeks, maternal use of nonsteroidal anti-inflammatory drugs/selective serotonin reuptake inhibitors, cardiovascular anomalies, intrauterine growth restriction). Labile hypoxemia (wide variations in arterial oxygen saturation because of rapidly changing PBF) and differential cyanosis (preductal oxygen saturation >5% higher than the postductal oxygen saturation as a result of right-to-left shunting across the PFO and PDA) are characteristic findings in PPHN. Differential cyanosis will be absent if the PDA is closed and/or in the presence of a significant intracardiac

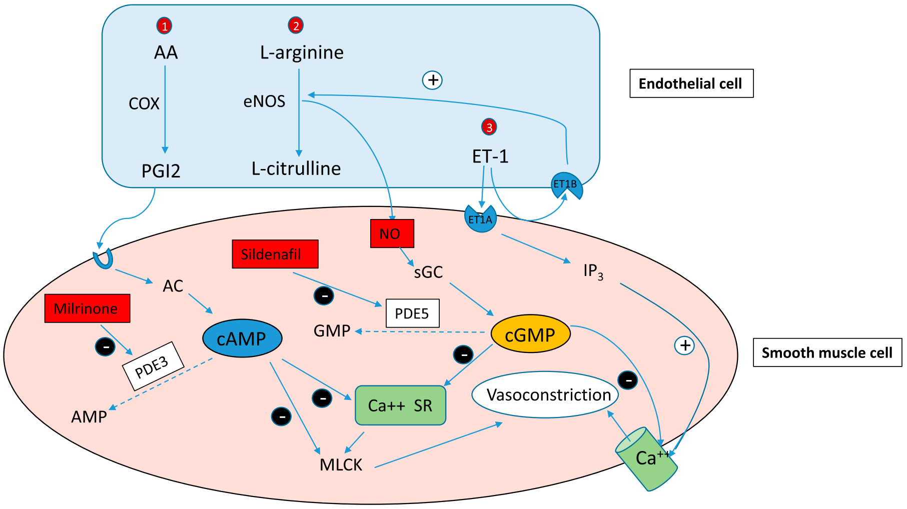

Figure 1. The interaction between the pulmonary endothelial cell and vascular smooth muscle cell. 1. Arachidonic acid (AA) pathway; 2. nitric oxide (NO) pathway; 3. endothelin-1 (ET-1) pathway. COX=cyclooxygenase; eNOS=endothelial nitric oxide synthase; PDE=phosphodiesterase; cAMP=cyclic adenosine monophosphate; cGMP=cyclic guanosine monophosphate; sGC=soluble guanylate cyclase; IP_3=inositol phosphate; MLCK=myosin light chain kinase; PGI2=prostacyclin.

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shunt. Patients typically present with symptoms of shock, called *"obstructive shock"* with tachycardia, prolonged capillary refill time (>3 seconds), oliguria, systemic hypotension, and lactic acidosis. A loud single second heart sound may be heard on physical examination along with a systolic murmur from tricuspid regurgitation. (13)

A thorough clinical evaluation with pertinent imaging is required for timely diagnosis of circulatory failure. Chest radiographs can help in differentiating the etiology (black or hypovascular lung fields are observed in neonates with idiopathic PPHN whereas infiltrates can be seen radiographically in patients with meconium aspiration syndrome/respiratory distress syndrome). The gold standard for diagnosing PPHN is echocardiography. Cardiac catheterization is the gold standard for all other types of pulmonary hypertension. (14) Echocardiographic findings of PPHN include right ventricular (RV) dilation, left-sided deviation of the interventricular septum, increased tricuspid jet velocity (used to calculate PAP using the modified Bernoulli equation), and right-to-left shunting across the PFO/PDA. Elevated right-sided pressures because of right heart failure and decreased left atrial pressures because of decreased pulmonary venous return may lead to right-to-left shunting across the PFO and decrease both the pre- and postductal SaO_2. In most cases, a low postductal SaO_2 alone (with normal preductal SaO_2) does not cause tissue hypoxia. In contrast, a decrease in the preductal SaO_2 is usually associated with symptoms of shock and an increased lactate concentration. (15) Echocardiography is also helpful to rule out congenital heart anomalies and to evaluate cardiac function, which may alter management. The oxygenation index (OI) is the most commonly used objective indicator of oxygenation in infants with PPHN. It is used to determine the clinical severity and guide therapeutic decision-making. (13)

$$\mathrm{OI} = FiO_2 \times \text{mean airway pressure (in cm } H_2O) \times 100/PaO_2 \text{ (in mm Hg)}$$

The primary goal of therapy is decreasing PVR (ie, inducing pulmonary vasodilation) and improving cardiac output. OI that is trending upward despite appropriate management represents worsening respiratory failure, necessitating additional interventions.

THE IDEAL AGENT FOR THE MANAGEMENT OF PPHN

The ideal medication for the management of PPHN should lead to a reduction in PVR with a corresponding decrease in RV afterload, decrease in the extrapulmonary and intrapulmonary shunt, and improve cardiac output with an associated increase in vital organ perfusion without increasing myocardial oxygen demand. Inhaled nitric oxide (iNO) is widely accepted as the agent of choice for the treatment of PPHN because iNO is a selective pulmonary vasodilator. (16) It is the only pulmonary vasodilator approved by the US Food and Drug Administration for infants with PPHN and has become the standard of care in infants with moderate to severe PPHN. (17) iNO works via the iNO-cGMP pathway with downstream effects on vascular smooth muscle cells by decreasing the influx of calcium. iNO decreases PVR, improves ventilation-perfusion mismatch, and decreases the need for extracorporeal membranous oxygenation (ECMO) in patients with severe PPHN. (18) iNO is typically started when the neonate's OI is between 15 and 25 and it is then titrated based on the arterial oxygen pressure.

Unfortunately, up to 40% of infants with PPHN do not respond to iNO. An OI greater than 40 despite iNO therapy is a poor prognostic factor and is the threshold for switching to ECMO. If ECMO is not available, mortality in these patients may be as high as 60% to 80%. (14)(19) There can be several reasons for a decrease or lack of response to iNO. Hyperoxia-mediated superoxide generation may blunt the response to iNO and also alter endogenous NO production by uncoupling eNOS. Decreased activity of soluble cGMP, a downstream mediator of the NO-cGMP pathway, has been described in a lamb model. Increased activity of cGMP-specific phosphodiesterase (PDE) in these patients may lead to rapid breakdown of cGMP. (5)

Alternative and/or supplemental agents to iNO are needed in the management of PPHN because of the high incidence of iNO nonresponsiveness, (20) adverse effects associated with prolonged use of high-dose iNO (methemoglobinemia, organ injury from elevated oxides, and cell membrane damage from peroxinitrites). (21)(22) Lastly, the limited use of iNO by air travel restricts iNO use for transportation by land only.

There is ongoing research to find adjunctive and alternate pulmonary vasodilators that may be used in iNO nonresponders and in resource-poor settings where iNO is not available. Sildenafil increases cGMP levels by inhibiting PDE5 and has been shown to improve oxygenation with and without concurrent iNO therapy. Prostacyclins increase cAMP levels by stimulating adenylate cyclase, and inhalational prostacyclin has been shown to improve oxygenation in a small case series of neonates who are refractory to iNO. (23) Data about endothelin-1 (a potent vasoconstrictor) receptor blockers such as bosentan in infants with PPHN are contradictory. (14) Milrinone is a PDE3 inhibitor that acts as a specific pulmonary dilator and will be discussed later in

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this review. Figure 1 summarizes the mechanisms of actions of the pulmonary vasodilators.

MYOCARDIAL DYSFUNCTION IN PPHN

In infants with PPHN, right and left ventricular function may be compromised because of increased right ventricular afterload (secondary to increased PVR) and decreased left ventricular preload (secondary to reduced pulmonary venous return). (15) Increased pressure in the dilated right ventricle shifts the interventricular septum toward the left side of the heart, which in turn decreases the LV filling capacity. This results in decreased LV cardiac output and systemic hypotension, which often requires vasoactive and inotropic agents. Animal data suggest that use of inotropes in PPHN that is associated with low cardiac output may raise the PVR (as well as the SVR), which may further compromise RV function. (24)(25) Peterson et al showed that there was increased morbidity and mortality in infants with low cardiac output in the setting of PPHN. (26) Figure 2 shows the vicious cycle of increased PVR, hypoxia-acidosis, and cardiac dysfunction that must all be taken into account when managing these cases.

THE PARADOX OF INOTROPES AND VASOPRESSORS IN THE MANAGEMENT OF PPHN

Traditionally, in infants with PPHN, neonatologists use inotropes and vasopressors to increase the systemic blood pressure/SVR and reverse the right-to-left shunting. There is generally hesitation to use afterload reducing agents to treat PPHN because of the concerns of systemic hypotension and a desire to maintain supranormal systemic arterial pressures (SAPs) in an attempt to reverse extrapulmonary right-to-left shunting. This traditional approach to maintain suprasystemic pressure does not focus on the primary physiologic maladaptation of the pulmonary vascular bed, which leads to increased RV afterload. This approach may result in harm because of many reasons. Firstly, the PVR may be so high that attempts to increase systemic pressure above PVR may require very high doses of inotropes and vasopressors. Such high doses of these agents (such as the α-receptor stimulating agents dopamine or epinephrine) will cause both peripheral and pulmonary vasoconstriction, which will further worsen the PPHN. Secondly, inotrope administration can induce tachycardia, which increases myocardial oxygen demand, potentially increasing the risk of apoptosis or necrosis of myocardial muscle. (25)(27) Finally, in some infants with PPHN, the ductus arteriosus may not even be patent; in these patients, instead of the intended goal of reversal of shunting aiding in increasing PBF, the increased SVR may lead to circulatory collapse. (28) Unfortunately, there is little evidence about which specific inotropic and vasopressor agents should be used in each patient, and once started what is the ideal initial dose, how to titrate the medication, and what parameters to monitor. A good understanding about the mechanisms of action of the commonly used agents is very important for using them in clinical practice.

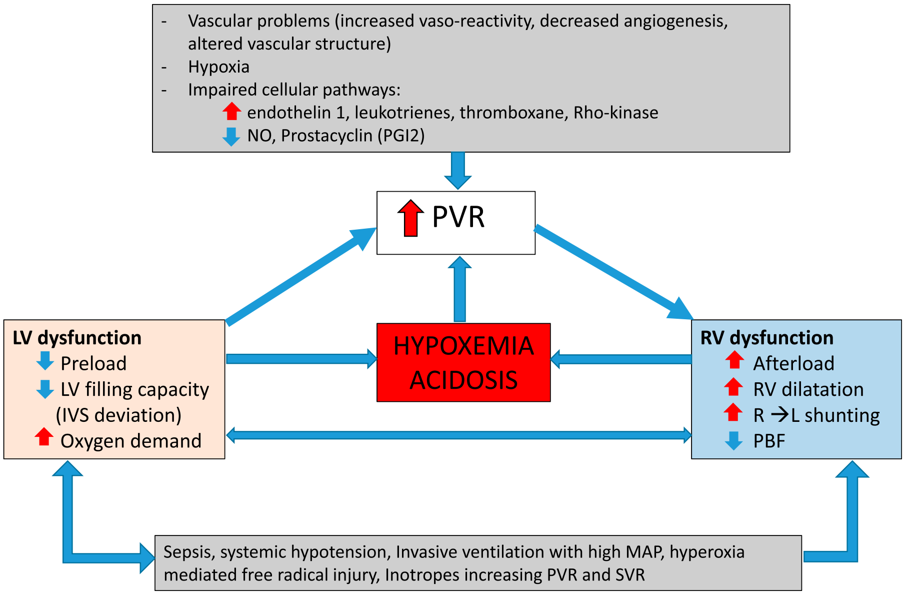
- Vascular problems (increased vaso-reactivity, decreased angiogenesis, altered vascular structure)
- Hypoxia
- Impaired cellular pathways:
⬆ endothelin 1, leukotrienes, thromboxane, Rho-kinase
⬇ NO, Prostacyclin (PGI2)
⬆ PVR
HYPOXEMIA ACIDOSIS
LV dysfunction
⬇ Preload
⬇ LV filling capacity (IVS deviation)
⬆ Oxygen demand
RV dysfunction
⬆ Afterload
⬆ RV dilatation
⬆ R → L shunting
⬇ PBF
Sepsis, systemic hypotension, Invasive ventilation with high MAP, hyperoxia mediated free radical injury, Inotropes increasing PVR and SVR

Figure 2. The vicious cycle of severe persistent pulmonary hypertension. IVS=interventricular septum; LV=left ventricular; MAP=mean airway pressure; NO=nitric oxide; PBF=pulmonary blood flow; PVR=pulmonary vascular resistance; RV=right ventricular; SVR=systemic vascular resistance.

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MECHANISMS OF ACTION

Inotropic agents primarily increase myocardial contractility by increasing intracellular calcium availability via stimulation of β-adrenergic and dopaminergic receptors on the cell membrane of myocardial cells. This leads to increased actin-myosin–mediated contractility. (5)(7)

Lusitropic agents increase myocardial relaxation by reducing intracellular calcium by cAMP-dependent activation of the inward pumping calcium channels or by promoting calcium dissociation from troponin C during diastole. (15)(24)

Vasopressor agents increase vascular tone. This increase in vascular tone is mediated by binding to α_1-adrenergic and vasopressin$_{1A}$ receptors that causes the activation of phospholipase C that in turn increases inositol triphosphate, leading to the release of calcium from the sarcoplasmic reticulum. (25)

Dopamine is the most commonly used inotropic agent in NICUs. It has dose-dependent effects via variable activation of $\alpha/\beta-$adrenergic and dopaminergic receptors. Low-dose dopamine (2–4 μg/kg per min) mainly stimulates the dopaminergic receptors that are selectively expressed in the renal, mesenteric, and coronary vasculature. (29) Moderate-dose dopamine (5–10 μg/kg per min) has inotropic and chronotropic effects via stimulation of cardiac β_1, β_2, and dopaminergic receptors. Higher doses of dopamine (>10 μg/kg per min) increase both SVR as well as PVR by stimulating vascular α_1-receptors, (25)(26) without an increase in cardiac output or possibly even a decrease in cardiac output. (30)(31) Of note, this description of the effects of dopamine at specific doses has not been studied well in neonates and is extrapolated from adult data; it is possible that neonates have different numbers of receptors, myocyte responsiveness, and variability in responsiveness based on gestational age and/or chronologic age. In critically sick infants, it is very important to monitor systemic blood pressure and organ perfusion at higher doses of dopamine. Liet et al measured pulmonary and systemic blood pressures and showed that dopamine has a variable effect on PVR depending on the baseline PBF (left-to-right shunt across PDA). (32) The authors found that dopamine increases PVR out of proportion to the increase in SVR in these patients. This could be because of the upregulation of pulmonary vasoconstriction by α_1 and endothelin receptor expression. Dopamine should be used with caution in infants with shunt lesions that may lead to pulmonary overcirculation because the increase in PVR may actually worsen PPHN.

Dobutamine increases myocardial contractility (inotropic), heart rate (chronotropic), and conduction velocity (dromotropic) and decreases SVR via β_1- and β_2-adrenergic receptor activity and increases SVR via α_1-adrenergic receptor activity. Adult data show that the cardiovascular effects of dobutamine are altered by the dose. At a very low dose (2–4 μg/kg per min), dobutamine has no significant hemodynamic effects. Moderate doses (5–10 μg/kg per min) have been shown to increase cardiac output and higher doses (10–20 μg/kg per min) have been shown to increase cardiac output as well as blood pressures, even in hypotensive preterm infants. (30)(31) Dobutamine is considered to be the drug of choice for infants with myocardial dysfunction and increased SVR (eg, perinatal asphyxia or preterm infants with poor systemic blood flow because of vasoconstriction during the fetal to neonatal transition period). However, higher doses of dobutamine may decrease ventricular compliance and LV filling in patients with myocardial hypertrophy (eg, in an infant of a diabetic mother with septal hypertrophy).

Epinephrine has also been shown to have dose-dependent cardiovascular effects in adults. It stimulates α- and β-adrenergic receptors in a dose-dependent manner. Extrapolating from adult data, at low doses (0.01–0.1 μg/kg per min), epinephrine causes inotropy, chronotropy, dromotropy, and peripheral vasodilation via stimulation of cardiac and vascular β_1- and β_2-adrenergic receptors. At doses greater than 0.1 μg/kg per min, it increases SVR (vasoconstriction) and inotropy via the stimulation of vascular and cardiac α_1-receptors, respectively. The net hemodynamic effects of epinephrine are increased blood pressure and systemic blood flow. (25) In clinical practice, epinephrine is useful in hypotensive infants with vasodilatory shock with or without myocardial dysfunction (eg, septic shock or asphyxia-related hemodynamic compromise).

Norepinephrine increases SVR and at the same time decreases PVR. (33) Norepinephrine causes systemic vasoconstriction via α_1- and α_2-receptor stimulation. Stimulation of α_2 also increases endogenous NO release in the pulmonary vascular endothelium. In an observational study of norepinephrine in infants with PPHN, Tourneux et al found that the use of norepinephrine significantly decreased the infant's oxygen requirement and the ratio of PAP to SAP. (34) This significant decrease in the PAP to SAP ratio is attributed to norepinephrine decreasing the PAP more than it increases the SAP. This suggests that norepinephrine may have potential beneficial effects for infants with PPHN.

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Vasopressin causes vasoconstriction in the skin, liver, and pancreas and vasodilation in coronary and pulmonary blood vessels via V1 receptor stimulation in the vascular smooth muscle cells. (19) In a case series of 10 term infants with severe PPHN refractory to iNO, vasopressin improved systolic blood pressure and decreased the OI. (35)

Milrinone is derived from the bipyridine amrinone via methylation and carboxylation and has a 15-fold increase in potency compared with the parent compound. (36) It is a nonglycoside noncatecholamine bypyridine compound that specifically inhibits PDE3, leading to increased cytosolic cAMP. It has 3 main effects: pulmonary vasodilation, enhanced myocardial contractility (inotropy), and enhanced myocardial relaxation (lusitropy).

Pulmonary Vasodilation

Inhibition of PDE3 in vascular smooth muscle cells (both arterial and venous) leads to increased cAMP levels. cAMP causes vasorelaxation by improving calcium uptake into the sarcoplasmic reticulum (Fig 1).

Milrinone administration also may exhibit synergism with iNO therapy. Because cAMP and cGMP have different mechanisms of action in vascular smooth muscle cells (Fig 1), it is likely that increasing the levels of both together may have a synergistic effect compared with an increase in levels of either one alone. Addition of milrinone to iNO therapy in canine and porcine experimental models shows a greater reduction in PAP and PVR than with iNO alone. (37) In a study in fetal lambs with PPHN induced by ductal ligation, Lakshminrusimha et al found that pretreatment with milrinone enhanced the effect of dilation of pulmonary arteries by prostacyclin and iloprost (both work by increasing cAMP levels). (38) PDE3 has high affinity for both cAMP and cGMP. Low levels of cGMP inhibit PDE3, decreasing the hydrolysis of cAMP. The synergistic effects of agents that increase both cAMP and cGMP (Fig 3) may be secondary to this interaction. (37) Exogenous NO has been shown to upregulate PDE3 in pulmonary vascular smooth muscle cells, resulting in loss or decrease of cAMP-dependent vasodilatory mechanisms. Addition of milrinone may restore these cAMP-dependent mechanisms.

Inotropy/Improved Myocardial Performance

Accumulation of cAMP in cardiac myocytes via selective inhibition of intracardiac PDE3 leads to improved calcium uptake, storage, and release from sarcoplasmic reticulum during excitation/contraction coupling, resulting in improved contractility.

A study in frog ventricular cells showed that increased cGMP (an effect of iNO) may antagonize the positive inotropic effects of catecholamines and cAMP by promoting cAMP hydrolysis via activation of cGMP-stimulated PDE. Even though these negative inotropic effects of iNO have never been reported in neonates or adults, (39) it is possible that the addition of milrinone in patients with PPHN can improve cardiac output by counteracting the negative inotropic effects of iNO.

In previous research, the positive inotropic effect of milrinone that was noted in neonatal canine and porcine models (40) was not demonstrated in a neonatal rabbit experimental model. (41) This inconsistency is attributed

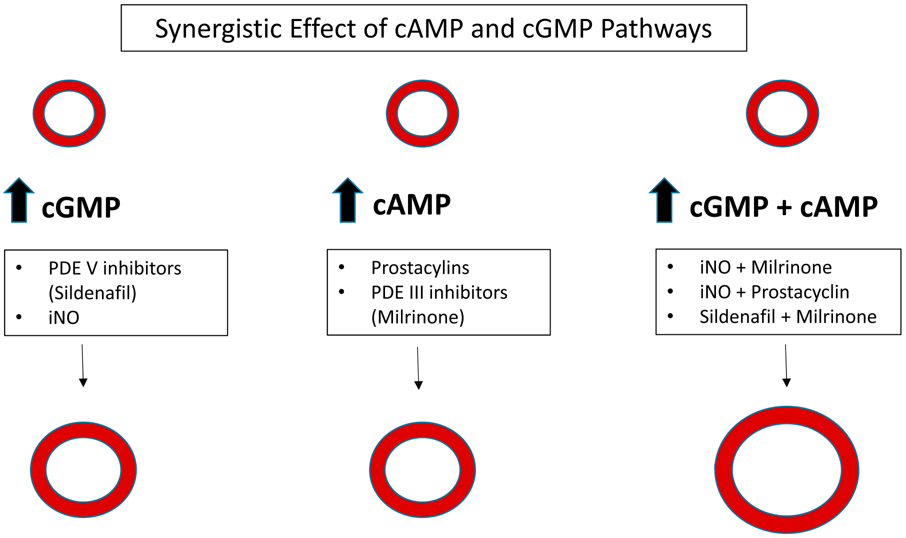
Synergistic Effect of cAMP and cGMP Pathways
cGMP
• PDE V inhibitors (Sildenafil)
• iNO
cAMP
• Prostacylins
• PDE III inhibitors (Milrinone)
cGMP + cAMP
• iNO + Milrinone
• iNO + Prostacyclin
• Sildenafil + Milrinone

Figure 3. The synergistic effect of milrinone and iNO. cAMP=cyclic adenosine monophosphate; cGMP=cyclic guanosine monophosphate; iNO=inhaled nitric oxide; PDE=phosphodiesterase.

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to the differences in the type of PDE expression in different species—PDE4 is the active enzyme responsible for cAMP metabolism in the fetal heart, and PDE3 (the target of milrinone) upregulation starts at birth.

Milrinone has been used to prevent low cardiac output syndrome in patients after cardiac surgery. The PRIMACORP trial (prophylactic intravenous use of milrinone after cardiac operation in pediatric patients, ranging in age from 2 days to 6.9 years) showed a 64% relative risk reduction in the development of low cardiac output syndrome with the prophylactic use of high-dose milrinone. (42) Chang et al studied moderate-dose intravenous milrinone (bolus of 50 μg/kg over 15 mins followed by infusion of 0.5 μg/kg per min) in 10 neonates (ages 3–21 days, median 5 days) and found a significant increase in cardiac index and right and left ventricular stroke work index, along with significant decreases in biatrial pressures, mean PAP, SVR, and PVR with milrinone use. (36) Bailey et al reported an increase in cardiac index with the use of milrinone in 3- to 22-month-old infants after cardiac surgery. (43)

In contrast to dopamine and epinephrine, milrinone increases cAMP levels in vascular smooth muscle cells independent of β-adrenergic receptors. Milrinone also improves myocardial performance without increasing myocardial oxygen demand.

Lusitropy

Milrinone reduces calcium concentration in cardiac myocytes by activating inward-pumping calcium channels (cAMP dependent) on the sarcoplasmic reticulum. It also improves actin-myosin dissociation by promoting the dissociation of calcium from troponin C during diastole. These are the mechanisms by which milrinone results in myocardial relaxation or lusitropy. (44)

THE ROLE OF PDE3 INHIBITORS SUCH AS MILRINONE IN PPHN

The Table provides a summary of the studies that have reported the use of milrinone in neonates with PPHN. A much-needed randomized controlled trial is currently ongoing (MINT-2014-0).

PDE3 INHIBITOR (MILRINONE) USE IN SPECIAL POPULATIONS

Preterm Infants

Milrinone has been shown to improve low systemic blood flow for the first 24 hours after birth in preterm infants. Paradisis et al conducted a pilot trial to study the pharmacokinetics of milrinone in increasing superior vena cava

TABLE. **Current Clinical Data on the Use of Milrinone in Neonates with PPHN**

REFERENCE	STUDY DESIGN	STUDY PARTICIPANTS	DOSE OF MILRINONE	SIGNIFICANT RESULTS
Bassler et al (51)	Case reports	4 (1 preterm, 26-wk GA)	Bolus: 50 μg/kg Infusion: 0.33 μg/kg per min	↓ OI
McNamara et al (55)	Case series	9 term infants	Bolus: none Infusion: 0.33–0.99 μg/kg per min	↓ OI
Patel (47)	Retrospective review	6 term infants	Bolus: none Infusion: 0.50–0.75 μg/kg per min	↓ OI
McNamara et al (52)	Open label study	11 term infants	Bolus: 50 μg/kg Infusion: 0.33–0.99 μg/kg per min	↓ OI, ↓ lactate, improved base deficit
James et al (49)	Retrospective review	17 infants >34 weeks' birth GA	Bolus: none Infusion: 0.50–0.75 μg/kg per min	↑ RV (4) function, ↓ OI ↓ PAP (5)
Giaccone et al (53)	Randomized open-label pilot study	6 infants >34 weeks' birth GA	Low dose with bolus of 20 μg/kg and infusion of 20 μg/kg per min (n=2) Standard dose with bolus of 50 μg/kg and infusion of 50 μg/kg per min	CL (6) 3.05 ml/min/kg ↑ CL with age ↓ OI (findings based on covariate model for both groups)

CL=clearance of milrinone; GA=gestational age; OI=oxygenation index; Term=GA ≥38 weeks; PAP=pulmonary arterial pressure; RV=right ventricular.

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flow (a marker of systemic blood flow). (45) The half-life of milrinone in preterm infants was found to be 10 hours. The optimized dosing regimen was studied in 10 infants: loading dose of 0.75 μg/kg per min for 3 hours followed by maintenance dose of 0.2 μg/kg per min until 18 hours. All 10 infants who received the optimized dosing maintained normal superior vena cava flow. (45)(46) It is important to note that there was no comparison group for this analysis. No significant adverse effects were reported.

Congenital Diaphragmatic Hernia

A retrospective study in 6 infants with congenital diaphragmatic hernia and severe PPHN showed a significant improvement in RV systolic and diastolic function (evaluated via tissue Doppler imaging) in addition to the significantly improved OI 48 to 72 hours after commencement of milrinone. (47) The mean PAP and bidirectional shunting across the PDA remained unchanged with milrinone therapy and the improvement in OI was attributed to the improved cardiac function rather than decreased PVR. No systemic hypotension was noted in these infants. Two infants received milrinone at 0.75 μg/kg per min and 4 received it at 0.5 μg/kg per min. No bolus doses were given. (47)

Hypertrophic Cardiomyopathy in Infants of Diabetic Mothers

We recently reported a case of hypertrophic obstructive cardiomyopathy in an infant of a diabetic mother in whom the use of milrinone precluded the need for ECMO. We proposed that milrinone led to LV relaxation and improvement in the diastolic filling. (48)

SAFETY PROFILE OF MILRINONE

The possible adverse effects of milrinone include systemic hypotension and increased risk of bleeding secondary to thrombocytopenia or inhibition of platelet aggregation. Only 1 study in neonates noted a significant decrease in mean arterial pressure in the first 6 hours after the bolus dose of milrinone but this was transient, and the blood pressure started increasing at 12 hours and was actually higher than baseline 72 hours after milrinone therapy was started. (49) Ramamoorthy et al reported some evidence of thrombocytopenia with milrinone use in over half of the treated children (ranging from 6 weeks to 11 years) who underwent cardiopulmonary bypass, though the effect was not life-threatening; 2 of 19 patients analyzed developed tachyarrythmia. (50) In a report of 4 cases, 2 patients (1 patient with a gestational age of 26 weeks) developed an intraventricular hemorrhage after milrinone therapy. (51) This adverse effect was not reported in any other study, including the PRIMACORP trial. However, data from a large-scale study of milrinone use in PPHN are lacking and it is prudent to keep these potential adverse effects in mind.

PHARMACOKINETICS AND DOSING OF MILRINONE IN PPHN

Studies have shown that the plasma clearance of milrinone improves with age; volume of distribution and half-life are higher in neonates. McNamara et al studied the pharmacokinetics in 11 infants (≥34 weeks' gestational age, ≤10 days after birth) with PPHN and found that the mean (± SD) half-life, total body clearance, volume of distribution, and steady state concentration of milrinone was 4.1 ± 1.1 hours, 0.11 ± 0.01 L/kg per hour (1.8 mL/kg per min), 0.56 ± 0.19 L/kg, and 290.9 ± 77.7 ng/mL, respectively. (52) A randomized open-label pilot study on the pharmacokinetics of milrinone included 6 term infants who were treated with 2 different dosing groups: low dose (20 μg/kg bolus followed by an infusion of 0.2 μg/kg per minute, n=2) and standard dose (50 μg/kg bolus followed by an infusion of 0.5 μg/kg per minute, n=4). (53) The authors calculated the clearance of milrinone to be 3.05 mL/kg per min and determined that the clearance increases with age. They found that the 1-day-old infant had higher concentrations of plasma milrinone compared with the 6-day-old infant. (53) In previous studies in infants after cardiac surgery in the PRIMACORP trial and neonates with hypoplastic left heart undergoing stage 1 reconstruction, the clearance has been reported to be 1.6 to 2.6 mL/kg per min. (43)(53) In a study of milrinone in preterm infants in the first 24 hours, the population mean clearance was 0.64 mL/kg per min. (46)

Based on these studies, the half-life of milrinone seems to be longer in preterm infants (∼10 hours) than term infants (∼4 hours) and children (1.47–3.15 hours). (45) Because of the longer half-life in neonates, it takes longer to achieve steady state levels and therefore a loading dose is recommended to achieve therapeutic concentrations earlier. Milrinone primarily undergoes renal excretion and 80% to 85% of the drug is excreted unchanged. In patients with impaired renal function, dose adjustment is necessary and loading doses should be avoided. The increasing clearance with age necessitates age-related dose adjustment as well.

The high dose used in the PRIMACORP trial (age of patients ranged from 2 days to 6.9 years) was a 75 μg/kg

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bolus over 60 minutes followed by an infusion of 0.75 μg/kg per min. In studies of neonates with PPHN, the typical loading dose has been 50 μg/kg followed by an infusion of 0.33 to 0.99 μg/kg per min (Table). All studies report a dose-dependent increase in efficacy. Only the intravenous route of administration has been studied in infants with PPHN. The use of inhaled milrinone has been shown to reduce PPHN and reperfusion syndrome in adults (≥18 years) after cardiopulmonary bypass. (54) The advantage of the inhaled form of milrinone is the lack of systemic hypotension. It would be prudent to study the role of inhaled milrinone in neonates with PPHN.

CONCLUSION

The use of milrinone in refractory PPHN has been supported by several studies because of its beneficial hemodynamic effects of improved biventricular function, improved oxygenation, and decreased PVR. However, evidence from randomized controlled trials is lacking. Milrinone use should be considered in iNO nonresponders before considering ECMO, with close monitoring of cardiovascular response using clinical parameters with serial functional echocardiography.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the various factors affecting oxygen uptake, transport, and delivery, including the blood and circulation.
- Know the factors affecting and regulating myocardial performance and function in the fetus and newborn infant and during the perinatal transitional period.
- Know the factors affecting and regulating the systemic circulation in the fetus (including umbilical vessels) and newborn infant during the perinatal transitional period.
- Understand the factors affecting and regulating the pulmonary circulation in the fetus and newborn infant and during the perinatal transitional period.
- Know the appropriate techniques to assess cardiovascular function in the fetus and newborn infant.
- Know the physiology of the ductus arteriosus and understand the factors affecting and regulating the ductus arteriosus in the fetus and newborn infant during the perinatal transitional period.
- Know the pathophysiology of a term or preterm infant with a condition affecting the systemic blood pressure, such as hypotension or hypertension.

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1. A newborn term infant is born via vaginal delivery after meconium-stained amniotic fluid is noted. Spontaneous cry is noted at birth, but the infant has respiratory distress, is resuscitated in the delivery room, and is brought to the NICU. The infant undergoes intubation and is placed on mechanical ventilation for persistent hypoxemia. Diagnostic evaluation and clinical course suggest that the infant has persistent pulmonary hypertension. Which of the following is most likely to be raising the pulmonary arterial pressure, thereby leading to hypoxemia in this infant?
   - A. Decreased pulmonary blood flow.
   - B. Decreased pulmonary capillary wedge pressure.
   - C. Persistently elevated pulmonary vascular resistance.
   - D. Rapid decrease in fluid in the lungs.
   - E. Relatively high oxygen content of air compared with intrauterine environment.
2. A term female infant is born via spontaneous vaginal delivery and gives a spontaneous cry soon after birth. The umbilical cord is clamped after 30 seconds and the infant is crying and appears to be transitioning appropriately. Over the next 5 minutes, the initial cyanosis fades and the infant is pink and appears comfortable in the mother's arms. Which of the following factors is a key contributor to the pulmonary vasodilation that has occurred in this infant, allowing for adequate oxygen delivery?
   - A. Nitric oxide production from increased activity of endothelial nitric oxide synthase.
   - B. Inhibition of the prostacyclin-cyclic monophosphate pathway.
   - C. Relatively early clamping of the umbilical cord.
   - D. Closing of the ductus arteriosus.
   - E. The microbiome content of the vaginal canal.
3. A term male infant has undergone the Fontan procedure for hypoplastic left heart syndrome. He is recovering after cardiac surgery and is receiving mechanical ventilation and several cardioactive medications. Which of the following drugs is characterized by pulmonary vasodilation, enhanced myocardial contractility, and enhanced myocardial relaxation?
   - A. Dopamine.
   - B. Dobutamine.
   - C. Epinephrine.
   - D. Vasopressin.
   - E. Milrinone.
4. A patient who has had repair of tetralogy of Fallot is recovering postoperatively and is noted to have pulmonary hypertension. The patient has been placed on several cardioactive medications, including milrinone. Which of the following is a known potential adverse effect of milrinone?
   - A. Hyperkalemia.
   - B. Severe hypertension.
   - C. Thrombocytopenia.
   - D. Profound sedation.
   - E. Grand mal seizures.

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5. An infant born at 34 weeks' gestational age has had surgery for complex congenital heart disease. She has low cardiac output syndrome and is being started on milrinone. Which of the following statements regarding pharmacokinetics and dosing of milrinone in neonates is correct?

   A. The half-life of milrinone is consistently shorter in preterm infants than in term infants.
   B. Milrinone will have a shorter half-life in neonates compared with older patients.
   C. A loading dose is absolutely contraindicated for the use of milrinone because of the potential for overdose and toxicity.
   D. Milrinone primarily undergoes renal excretion and 80% to 85% of the drug is excreted unchanged.
   E. The study of inhaled milrinone in adult patients has shown a paradoxical effect of increased pulmonary hypertension and higher incidence of systemic hypotension.

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Quality Improvement in Congenital Heart Surgery

Timothy W. Pettitt, MD*†

*Department of Pediatric Cardiovascular Surgery, Children's Hospital of New Orleans, New Orleans, LA
†Department of Surgery, Louisiana State University Health Science Center, New Orleans, LA

Practice Gaps

Factors contributing to high-quality surgical outcomes for patients with congenital heart disease extend beyond the surgeon alone. They depend on the combined performance of the entire multidisciplinary team, supported by robust organizational structures and workflow processes. Prenatal diagnosis of certain types of congenital heart disease is critically important to coordinate care and facilitate delivery at a center capable of providing specialized care and intervention.

Abstract

Congenital heart disease is a major public health concern in the United States. Outcomes of surgery for children with congenital heart disease have dramatically improved over the last several decades with current aggregate operative mortality rates approximating 3%, inclusive of all ages and defects. However, there remains significant variability among institutions, especially for higher-risk and more complex patients. As health care moves toward the quadruple aim of improving patient experience, improving the health of populations, lowering costs, and increasing satisfaction among providers, congenital heart surgery programs must evolve to meet the growing scrutiny, demands, and expectations of numerous stakeholders. Improved outcomes and reduced interinstitutional variability are achieved through prioritization of quality assurance and improvement.

Objectives

After completing this article, readers should be able to:

1. Appreciate the role that organizational culture, commitment to continuous quality improvement, and participation in national databases plays in achieving high-quality care.
2. Recognize how implementation of intraoperative expanded timeouts and structured operating room–to–cardiac intensive care unit handoffs can strengthen care teams, as well as improve safety and quality through improved communication and engagement.
3. Be aware of current anesthesia and perfusion strategies to improve outcomes in the operating room.

AUTHOR DISCLOSURE Dr Pettitt has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CCAS	Congenital Cardiac Anesthesia Society
CHD	congenital heart disease
CICU	cardiac intensive care unit
CPB	cardiopulmonary bypass
DHCA	deep hypothermic circulatory arrest
d-TGA	d-loop transposition of the great arteries
EASE	Electronic Access to Surgical Events
ECMO	extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
HLHS	hypoplastic left heart syndrome
HSM	home surveillance monitoring
M&M	morbidity and mortality
NPC-QIC	National Pediatric Cardiology Quality Improvement Collaborative
OR	operating room
PAC	pediatric advanced care
RBC	red blood cell
STS	Society of Thoracic Surgeons
STSCHSD	Society of Thoracic Surgeons Congenital Heart Surgery Database

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4. Describe the impact that having a dedicated pediatric cardiac intensive care unit team has on outcomes by incorporating multidisciplinary care models, standardized management protocols, 24/7 in-house intensivist coverage, and nursing education.
5. Recognize the impact of a comprehensive home surveillance monitoring program on reducing interstage mortality for high-risk infants after stage 1 Norwood procedure.

INTRODUCTION

Congenital structural heart disease is the most common birth defect, involving nearly 1% of births (approximately 40,000) per year in the United States. (1) With improved long-term survival, there are more adults than children now living with congenital heart disease (CHD). Patients with CHD represent a relatively small population, yet consume a disproportionate amount of medical resources and expenditures based on disease severity and impact across the lifespan of patients. Escalating health care costs, public reporting, and scandals have encouraged the media and the public to focus on health care quality. Furthermore, health care is transitioning "from a system of payment based on the volume or *quantity* of services provided (fee-for-service) to payment based on the value of those services (value-based care, pay-for-performance, and alternative payment models)."(2) As such, there are powerful incentives, both ethical and practical, for clinicians and health care organizations to deliver high-quality services. This narrative review is intended to provide an overview of current strategies to measure and improve the quality of care for patients undergoing congenital heart surgery.

MEASURING QUALITY

The Donabedian model, proposed in 1966, is the primary paradigm currently used to assess the quality of health care. (3) Based on this model, data on the quality of care can be inferred from 3 categories: structure, process, and outcomes. Structure encompasses all of the characteristics that affect the context within which care is delivered. This includes the physical space, equipment, and human resources as well as the features of the organization such as governance, management, staff training and education, and culture. Process involves all acts of health care delivery: what is done (diagnosis, treatment, preventive care, and patient education) and how it is done (technical, workflow, and interpersonal processes). Outcome is the final product of health care delivery, encompassing mortality, morbidity, quality of life, patient satisfaction, and cost. Although outcomes are, perhaps, the most important and intuitive measure of quality, they can be difficult to exclusively attribute to health care processes.

Starting in 2007, and revised in 2011, the Society of Thoracic Surgeons (STS) developed and approved "Quality Measures for Congenital and Pediatric Cardiac Surgery," which were endorsed by the Congenital Heart Surgeons' Society. (4) These quality measures, which were based on the Donabedian triad, were developed for use by centers as a tool to standardize practice and facilitate quality improvement initiatives with the overarching goal of reducing variability of outcomes across programs. This review will explore and expand upon these original structural and process measures proposed by the STS that increase the likelihood of delivering high-quality care in congenital heart surgery.

STRUCTURAL MEASURES

Organizational Culture

Culture, more than anything else, drives performance, quality, and financial optimization. Organizational culture depends on the collective and overriding attitudes, values, and behaviors of all hospital personnel at all levels. Leadership, both administrative and clinical, is of paramount importance to define and disseminate the organization's core values and goals as well as to create an environment that enables and encourages teamwork, collaboration, transparency, and trust. Engagement is important to an organization's success because a committed and unified workforce is far more likely to deliver high-quality, compassionate, and efficient care. Empowering every member of the care team to be an active participant will go a long way to achieve goals and outcomes that are in the best interest of patients, coworkers, the organization, and community at large.

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Commitment to Quality Assurance and Improvement

Congenital heart surgery programs must fully embrace quality and safety by promoting a culture of continuous assessment and improvement across all aspects of the program. This requires a regular venue for team members to come together, identify quality issues, and develop solutions. Plan-Do-Study-Act cycles are a particularly useful quality improvement tool for care teams to solve problems by developing an intervention to effect change (Plan), testing or carrying out the intervention (Do), observing and learning from the consequences (Study), and determining what modifications should be made to achieve the desired outcomes (Act). (5)

Morbidity and mortality (M&M) conferences should occur on a regular basis (typically monthly) to review deaths and major complications. The overriding theme of the M&M conference should not be to assign blame or seek absolution but rather to have an open discussion of the circumstances that led to the adverse outcomes and plans to prevent similar problems from happening in the future. In addition to M&M conferences, there should also be a venue for the program to compare its outcomes (morbidity, mortality, length of stay) to national aggregates and benchmark data. This requires participation in at least 1 national database that provides frequent summaries comparing an individual center's data with national multicenter aggregates. (4) Having a dedicated data/quality assurance manager facilitates the assimilation of data and presentation to the entire team for review on a quarterly, biannual, or annual basis.

Participation in Clinical Databases and Registries

Participation in multicenter databases has become a fundamental component of care for patients with CHD. The primary function of databases and registries has always been to benchmark outcomes and define standards at a national or worldwide level against which individual centers can measure their performance and focus on quality improvement initiatives. Collaborative learning efforts and research can be used to tease out specific elements of care associated with improved outcomes, which can then be disseminated to reduce variation and improve outcomes among centers. There are more than 30 multicenter databases or patient registries focused on CHD worldwide, and these involve surgery, intensive care, cardiology and anesthesia. (6) Two of the most relevant are described herein.

STS National Database. In 1989, the STS national database was created as a platform for quality improvement and patient safety for cardiothoracic surgeons. (7) The STS Congenital Heart Surgery Database (STSCHSD) component, established in 1994, is the largest database in North America dedicated to neonates, infants, children, and adults with congenital cardiac malformations. The most recent Spring 2019 STSCHSD report includes data from 118 North American STSCHSD participants representing 127 hospitals, accounting for approximately 95% of hospitals performing congenital heart surgery. (8)

The database divides patients by procedure, age group (neonate, infant, child, adult), and complexity. The main complexity adjustment tool for the STSCHSD is the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories or STAT. The STAT method divides patients into 5 strata with STAT-1 being the least complex to STAT-5 being the most complex. The Table provides examples of common types of surgery and current mortality rates within each STAT category. Operative mortality is risk (case-mix) adjusted to allow for comparison, in a uniform way, of hospitals that treat different populations of patients (mix of prematurity, low birthweight, procedure type, noncardiac congenital anatomic abnormalities, prior cardiac operation, chromosomal abnormalities, and syndromes) and disease severity or preoperative risk factors (preoperative mechanical circulatory or ventilatory support, shock, renal failure, or neurologic deficit). Data on 10 common benchmark operations and nine specific lesions are also reported.

A major transformation is coming to the STSCHSD in early 2020. The Society has partnered with a leading provider of technology solutions to help speed innovation, incorporate a cloud-based system, offer rapid data access, and new dashboard reporting. Ongoing and future quality initiatives of the STSCHSD include (9):

- Incorporation of a composite quality measure that includes both M&M domains. (10) The morbidity domain includes postoperative length of stay and major complications (renal failure requiring dialysis, neurologic deficit at discharge, arrhythmia treated with a pacemaker, mechanical circulatory support, diaphragm paralysis, unplanned cardiac reoperation, reoperation for bleeding, and cardiac arrest). This measure has greater capability to provide a more comprehensive view of quality than mortality alone and discriminate programmatic performance
- More granular risk adjustment for chromosomal abnormalities, genetic disorders, and noncardiac congenital anomalies
- Revision and upgrading of the existing STAT mortality categories and scores
- Defining cohorts of patients combining diagnosis (lesion specific) with procedure type
- Linkage of STSCHSD to national mortality databases for long-term longitudinal follow-up

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TABLE. Common Types of Surgery Within Each STAT Category

STAT CATEGORY (ALL AGES)	OPERATION	STS OPERATIVE MORTALITY RATE (%)
1	ASD repair, VSD repair, subaortic stenosis resection, pulmonary valve replacement, conduit replacement	0.4
2	Tetralogy of Fallot repair, bidirectional Glenn shunt, Fontan operation, Ross operation, coarctation (extended end-to-end) repair	1.5
3	CAVC repair, arterial switch operation, hemi-Fontan, Rastelli operation	2.1
4	Interrupted aortic arch repair, arterial switch operation with VSD closure, heart transplant, aortopulmonary shunt, total anomalous pulmonary venous return repair, truncus arteriosus repair	6.3
5	Norwood (stage 1) operation, hybrid stage 1 procedure, double switch, truncus arteriosus with interrupted aortic arch repair	13.9
All		2.8

STS operative mortality rate based on STAT category for 2015-2018 Harvest data of the STS Congenital Heart Surgery Database.(8) ASD=atrial septal defect; CAVC=complete atrioventricular canal; VSD=ventricular septal defect; STAT= Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories; STS=Society of Thoracic Surgeons.

Pediatric Cardiac Care Consortium. The Pediatric Cardiac Care Consortium, formed in 2009 with National Institutes of Health funding, is a unique national database composed of leaders in pediatric cardiac critical care, cardiac surgery, and cardiology with the aim to improve the quality of care for patients with CHD. It is a "multi-institutional collaboration committed to discovery through transparent sharing of data. By providing 24/7 access to real-time, high-quality and actionable outcome data, member institutions can benchmark performance and identify opportunities for local quality improvement initiatives."(11) Some of the quality metrics available for comparative analyses include mechanical ventilation time, reintubation, unplanned extubations, hospital and cardiac intensive care unit (CICU) length of stay, infections, number of days with invasive vascular access, acquired complications, need for surgical reintervention, and CICU mortality.

Public Reporting

Public reporting of outcomes is becoming increasingly common worldwide, with reporting being mandatory in the United Kingdom. While being a transparent and easily accessible source of information for families, public reporting and ranking of hospitals has the tendency to steer patients toward high-performing centers. This might be a stimulus for lower-performing centers to participate in quality improvement initiatives and reduce interinstitutional variability, but it may also have the unintended consequence of programs becoming risk averse.

STS Database Public Reporting. In January 2015, the STS began a program of voluntary public reporting of risk-adjusted outcomes. As of 2018, 85% of enrolled STSCHSD participants agreed to publicly report their outcomes. "A 'star' rating system is used to highlight programs whose outcomes differ significantly from their calculated expected risk-adjusted outcomes." (6) *One-star* programs have higher than expected operative mortality, *two stars* have expected operative mortality, and *three stars* have lower than expected operative mortality. As of 2018, approximately 83% of programs are rated two stars with 8% being one- or three-star(s). (8) The star rating system has been under increasing scrutiny and criticized as being too simplistic and an inaccurate representation of extremely complex data. The public reporting process is currently under review and expected to change. Possible changes include reporting outcomes for specific, benchmark operations rather than an aggregate of all STAT categories and ages (as is currently used for star rating) and assigning center-specific case mix indices.

US News and World Report. This is a publication that annually ranks US children's hospitals and major pediatric subspecialties, including pediatric cardiology and heart surgery. "Their independently derived ranking algorithm assigns 'points' to a variety of structure, process, and outcome metrics." (6) Rankings rely primarily on objective data collected

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via self-reported answers by hospitals to a detailed clinical survey. Hospitals are scored based on 4 elements: outcomes (including survival rate and rate of discharge from the hospital after complex heart surgery), patient experience (based on family satisfaction surveys), care-related factors (patient volume, breadth of specialized staff, services, technologies, commitment to best practices, and ability to prevent infection), and expert opinion obtained from pediatric heart specialists. (12)

Availability of Extracorporeal Membrane Oxygenation

In the 4-year period extending from January 2015 to December 2018 there was a 0.4% aggregate mortality rate for the lowest complexity cases (see STAT category 1, Table). (5) Approximately 0.1% of patients with a secundum atrial septal defect and 0.2% of patients with a perimembranous ventricular septal defect who underwent surgery also required extracorporeal membrane oxygenation (ECMO). This underscores the importance of having ECMO support, even in low-volume centers performing low-complexity cases. The Extracorporeal Life Support Organization (ELSO) recognizes centers that have processes, procedures, and systems to provide exceptional ECMO care. ELSO's Award for Excellence demonstrates programmatic assurance of high quality standards including specialized equipment and supplies, specific patient protocols, and advanced training of all staff. (13)

Surgical Volume and the Case for Regionalization of Care

Cardiac surgical programs must "maintain adequate case volumes to achieve and demonstrate high-quality outcomes." (14) Several studies have demonstrated a significant inverse association between pediatric cardiac surgical volume and mortality. (15)(16)(17) Although volume alone was an unreliable discriminator of mortality, mortality rates adjusted for patient risk factors and surgical case mix suggest that, in aggregate, higher-volume programs achieve lower mortality rates for more complex operations such as the Norwood procedure. Other studies demonstrate less of a volume-outcome relationship, especially in the more recent era. (18)(19) Whether a volume-outcome relationship exists remains controversial, because of the wide variation among institutions. Some large programs have higher than expected mortality rates and many small programs have lower than expected mortality rates. It has been suggested that "high surgical case volume may be a surrogate or proxy for aspects of care that are more likely to be provided at larger centers but are not necessarily exclusive to these centers."(20) Higher-volume centers are more likely to have structural characteristics and engage in process measures that lead to better outcomes such as a dedicated intensive care unit (ICU), multidisciplinary team approach, and more experienced pre-, intra- and postoperative decision-making and care. These measures are discussed further in subsequent sections of this review.

There are approximately 125 hospitals in North America performing congenital heart surgery. Given the significant variation in mortality, morbidity, and length of stay across these hospitals, regionalization or centralization of care has been proposed as a potential solution to improve outcomes. Several countries, including Sweden, the Netherlands, and the United Kingdom have developed or proposed consolidation of care for children with CHD at select high-volume, high-quality hospitals. (21) A theoretical analysis of the effects of regionalizing care in California demonstrated a small, albeit important, reduction in mortality when all cases were referred to high-volume hospitals. (22) A recent study in the United States investigated hospital locations and patient travel patterns for congenital cardiac surgery. (21) Sixty-six percent of hospitals were located within 25 miles of another hospital. Many patients travel long distances for surgery to larger centers where better care is presumed, with 25% of patients traveling more than 100 miles, and 53% circumventing their nearest hospital. The frequent geographic clustering of pediatric cardiac surgical hospitals in the United States (particularly smaller-volume centers that are located near larger centers) coupled with the fact that patients are already traveling significant distances for care, makes a case for regionalization of care in this country. Furthermore, as health care reform decreases reimbursements and encourages hospitals to coordinate care, larger pediatric cardiac surgical programs may benefit from the economies and efficiencies of scale. Therefore, "a planned network of fewer, high-volume/high-quality hospitals with ample resources and comprehensive infrastructures may hold the potential to reduce variation in care and improve outcomes." (21)

Patients with end-stage heart failure who require ventricular assist device therapy and/or cardiac transplantation represent a relatively low-volume, high-risk population. Many, but not all cardiac heart surgery centers provide these services; however, consolidation of care for these patients at major transplant centers seems reasonable given the limited donor supply and resources required.

PROCESS MEASURES

Prenatal Diagnosis and Care

The Centers for Disease Control and Prevention and the National Birth Defects Prevention Study found that only 15% of mothers with a child with a congenital heart defect reported that they first learned about their infant's

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condition during pregnancy. (1) This is alarmingly low. For many congenital heart defects, it is imperative that the diagnosis be made prenatally, to facilitate early intervention and reduce serious complications after the child is born. Numerous studies have demonstrated improved outcomes with prenatal diagnosis for patients with critical congenital heart disease. (23)(24) Patients with predominately ductal-dependent pulmonary or systemic blood flow are at particularly high risk for acute cardiorespiratory compromise and death if not recognized and treated early. This includes patients with hypoplastic left heart syndrome (HLHS) and other single ventricle variants, interrupted aortic arch, critical aortic stenosis and coarctation, critical pulmonary stenosis or atresia, and d-loop transposition of the great arteries (d-TGA). Other non–ductal-dependent defects, such as total anomalous pulmonary venous return, and congenital complete heart block require urgent intervention as well. Prenatal diagnosis of these defects allows parental counseling and education as well as planning of health care strategies before the infant is born. It is important for congenital heart surgery programs to establish regional outreach and networks to help train and support ultrasonographers, obstetricians, and maternal-fetal medicine specialists to increase their prenatal detection of CHD. Well-known risk factors for surgical mortality in neonates requiring cardiac surgery are low birthweight and prematurity. Every effort should be made to ensure adequate prenatal care and educate pregnant women about the “modifiable” risk factors that are associated with prematurity and low birthweight.

In high-risk patients with CHD, the outcome is dependent on the distance needed to travel from the birth facility to a hospital capable of performing urgent intervention and providing expert cardiac intensive care. Pregnant women should be transferred to facilities capable of providing immediate care to the neonate upon delivery, with rapid placement of umbilical lines, initiation of prostaglandin, hemodynamic and respiratory stabilization, echocardiography, and catheter-based and/or surgical intervention as needed. Even with initiation of prostaglandin and maintenance of ductal patency, some patients with d-TGA require urgent balloon atrial septostomy to improve oxygenation. The rare patient with HLHS and intact atrial septum may require ex utero intrapartum–to–ECMO or immediate surgical septostomy to survive. These are just 2 examples of patients who would not survive if delivered at a rural community hospital remote from a congenital heart surgery program.

To facilitate and coordinate perinatal care, many congenital heart surgical programs have developed regularly scheduled *multidisciplinary perinatal conferences* to discuss prenatal diagnoses, timing and mode of delivery, and services required. Families are encouraged to consult with specialists, tour the facility, and visit the ICU where their newborn will receive care. For patients who are born remotely, an experienced transport service is necessary to deal with the unique challenges of transporting newborns with critical CHD. (25)

Finally, early prenatal diagnosis of CHD may allow in utero intervention for fetuses with severe CHD, though its clinical application remains uncertain. Only approximately 5% of fetuses with major CHD are likely to benefit from this pioneering approach. Fetal semilunar valvuloplasty, opening and stenting of a restrictive atrial foramen in HLHS, and percutaneous implantation of a miniaturized pacemaker to treat complete heart block are examples of fetal cardiac therapy. (26)

Preoperative Care

Location of preoperative care for patients with CHD in a *dedicated specialized CICU* versus a general NICU/pediatric ICU varies significantly, both between and within institutions. In one multi-institutional study, preoperative care in a dedicated CICU was associated with lower mortality, especially in high-complexity operations and at high-volume centers. Preoperative and total hospital length of stay as well as length of mechanical ventilation were also significantly decreased. (27) In another more recent and larger multi-institutional study, patients admitted to a dedicated CICU also had similar findings of shorter preoperative, postoperative, and total hospital length of stay as well as fewer days of mechanical ventilation. Mortality rates did not differ but total hospital costs believed to be related to decreased infectious complications and more efficient resource use were significantly decreased. (28) These studies make a strong case for managing pre- and postoperative CHD cases in the same dedicated CICU.

What are the elements of a specialized unit, dedicated exclusively to a cohort of perioperative patients with CHD, that drive better outcomes at lower costs? Continuity of care with fewer handoffs and less information loss is one element. Other factors are more efficient use of resources, adherence to standardized protocols, and implementation of a multidisciplinary team approach. These concepts will be explored in more detail in the postoperative section; however, “the combined experiences and iterative learning by groups of clinicians may account for the observed differences in length of stay and cost. It is possible that the real message in this research is the potential for groups of clinicians, with experience of the complete patient journey, to work

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together to develop individual expertise and to evolve and adapt the care environment, care processes, and tools." (29)

It is imperative to have a well-structured *preoperative multidisciplinary case management conference*. This conference should be attended by surgeons, cardiologists, anesthesiologists, and intensivists, at a minimum, but all members of the heart center team are encouraged to attend. Videoconferencing has become a valuable tool to allow outside referring cardiologists to engage with the team and present patients for surgical consideration. This conference is also a great educational opportunity for students, residents, and fellows who also may be involved in conference preparation and presentation. The purpose of this conference is to systematically review the patient's history and physical examination findings; discuss the patient's clinical course; and review all pertinent imaging, hemodynamic, and laboratory data. This presentation is then followed by an open discussion of the surgical and/or medical plan of care. This is the time for every member of the team to weigh in, discuss options, share ideas, voice concerns, and consider the risks and benefits of intervention. Not only is this good for the patient but it empowers every member of the team to be an active participant in the care and management of the patient. This conference is typically held weekly but may occur more frequently to discuss add-ons or patients who require urgent surgical intervention before the next regularly scheduled conference.

Intraoperative Care

It is hard to imagine a more stressful, high-acuity, dynamic, and complex environment than the cardiovascular operating room (OR). For patients to have a safe, effective, and efficient journey through the OR, carefully designed processes must exist, which promote communication, cooperation, and coordination. To achieve this, health care has sought to emulate other high-reliability industries and models such as aviation, nuclear power, and Formula 1 pit-stop racing. (30)(31)(32) In each of these industries, a multidisciplinary team needs to come together as a single unit to effectively perform complex tasks in a stressful, high-risk, and time-sensitive environment. Lessons learned from these models applicable to health care include using checklists and briefings before and after surgery; training, simulation, and repetition; task allocation and sequencing; predicting, anticipating, and planning; adherence to disciplined, composed, and nondisruptive atmospheres and behaviors; and embracing an organizational culture of safety through continuous education and quality improvement with input from all team members.

Some examples of quality improvement initiatives being incorporated into ORs across the nation include expanded timeouts and structured handoffs. A universal protocol was introduced by the Joint Commission in 2004 and has become a mandatory quality standard. The universal protocol has 3 components: a preprocedural process to verify correct patient identity, surgical site marking, and a surgical timeout that occurs immediately before the procedure. (33) The surgical timeout process, especially in cardiac surgery, has evolved over the years to include more comprehensive, or enhanced, pauses occurring before, during, and after the procedure. (34)(35)(36) An *expanded/extended timeout* checklist for cardiac surgery includes a discussion of the operative plan, anesthetic goals, perfusion strategies, anticipated problems, required implants, equipment, and medications. Opening lines of communication between team members will strengthen and enhance team performance. Debriefing and after-action review have emerged as important components of the expanded timeout process. This gives the OR team an opportunity to pause after the procedure is complete to discuss the conduct of the operation and identify future targets for quality improvement. What went wrong? How can we do better?

Patient handoffs, or transitions between medical teams or units, are a particularly vulnerable period for errors to occur because of breakdowns in communication. The World Health Organization and Joint Commission recommend a standardized process to decrease errors related to handoffs. (33) Several studies have found that adherence to a *structured handoff process* between the OR and pediatric CICU after CHD can decrease communication errors and omissions and potentially improve patient outcomes. (30)(32) After a patient is admitted to the CICU following surgery, a brief period is required to assess the infant's vital signs, secure the airway, connect the ventilator and monitors, transfer infusions, and place chest tubes to suction. Mandatory attendance by the surgeon, anesthesiologist, intensivist, respiratory therapist, and critical care nursing is required to initiate the handoff process. Every effort is made to establish a quiet, controlled environment free of distraction to focus and engage every member of the team. The surgeon and anesthesiologist then take turns with an organized presentation of the patient's history and operative course based on a standardized checklist or protocol, which is filled out by the OR personnel before transferring the patient. Typical elements of a handoff checklist should include:

- Patient age, weight, diagnosis, pertinent medical/surgical history
- Anesthesia, surgical, and perfusion details
- Postoperative echocardiography results

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- Blood products given
- Current medication infusions
- Most recent laboratory results (arterial blood gas, hemoglobin/hematocrit, lactate, coagulation)
- Times of last opioid medications, muscle relaxants, and antibiotics
- Problems encountered during the case including airway/ventilation issues, excessive bleeding, and dysrhythmias.

It is imperative that the handoff process conclude with a discussion of the plan of care by the intensivist with the critical care team including anticipated problems, goals, and expectations, as well as an opportunity for questions.

The major goal of expanded timeout and handoff processes is to "create a cognitive picture of the patient that will translate into effective decision-making," situational awareness, and error prevention for all team members. (37) These processes have the added benefits of encouraging and engaging every member of the team to be an active participant in patient care. Quality improvement initiatives such as timeouts and handoffs are relatively simple and quick to execute, yet can have a profound impact on patient safety and outcomes.

Electronic Access to Surgical Events (EASE) is a text messaging platform compliant with the Health Insurance Portability and Accountability Act of 1996 that allows clinicians to send real-time updates on patients, including photos and videos, to their families via text messages. By providing frequent updates, EASE allows family members to stay connected with their child throughout the surgical procedure or ICU stay, reducing anxiety and building trust. Implementation of the EASE application has been shown to enhance the family experience and improve satisfaction. (38)(39)

Anesthesia

Anesthesiologists caring for patients with CHD require a high level of expertise and most congenital heart surgery programs use specially trained pediatric cardiac anesthesiologists. The Congenital Cardiac Anesthesia Society (CCAS), established in 2005, was formed within the Society for Pediatric Anesthesia to meet the growing demand for the highly specialized care required for these patients. As of 2009, a registry for the CCAS was incorporated into the STSCHSD and tracks multiple anesthesia-related metrics. This allows participants in the database to compare their anesthetic techniques and strategies to those at other centers for local quality improvement. Several examples of anesthesia-driven quality improvement initiatives are:

- Preference for radial arterial and jugular venous access versus femoral access to reduce the incidence of catheter-related bloodstream infections as well as to preserve femoral vessels for future catheterization and surgical access.
- Using ultrasonographic guidance for percutaneous arterial and venous access to reduce the number of access attempts and catheter-related complications such as pneumothorax, hemorrhage, inadvertent arterial puncture, and catheter malpositioning. (40)
- Changes in operative and postoperative analgesia-sedation to facilitate earlier extubation, either in the OR or soon after surgery (<6 hours from time of admission to ICU). Use of nonopioid agents, such as dexmedetomidine and propofol are becoming increasingly more popular to reduce opioid and benzodiazepine exposure in the OR. (41)(42) Advantages of early extubation include reduction of ventilator-related complications and other morbidity, reduction in ICU sedation requirements, early transition to enteral feeding, and improved hemodynamics after certain operations (eg, Glenn shunt, Fontan procedure), all of which translate into better outcomes and shorter ICU/hospital length of stay.

Perfusion

Current favorable short- and long-term outcomes after repair of complex CHD in neonates and infants would not be possible without the improvement and refinement of cardiopulmonary bypass (CPB) technology and techniques. Recent innovations in perfusion and CPB for congenital heart surgery have focused on minimization of red blood cell (RBC) and other blood product transfusion; selective regional perfusion; anticoagulation management; and myocardial protection. (43)

Minimization of RBC and Other Blood Product Transfusions. By convention, the unfavorable disparity between the pediatric patient's blood volume, especially neonates and infants, and the CPB circuit priming volume has necessitated the addition of packed RBCs to the priming solution to avoid excessive hemodilution. Neonates and infants are particularly vulnerable to the deleterious effects of RBC transfusion, including acute lung injury, immunomodulation, and thrombotic complications that can increase patient M&M. Transfusion, especially during CPB, has been associated with longer mechanical ventilation times and ICU length of stay. Although homologous RBC transfusion is often unavoidable for pediatric patients undergoing cardiac surgery, multiple techniques are currently being used to minimize the volume transfused and number of donor exposures(43)(44)(45)(46)(47)(48)(49)(50):

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- Retrograde autologous priming and acute normovolemic hemodilution are useful techniques for older children and adults. (44)
- Modified ultrafiltration is routinely used after bypass to hemoconcentrate and extract inflammatory mediators. Modified ultrafiltration has been shown to "decrease total body water accumulation, increase mean arterial pressure, improve left ventricular systolic function and improve pulmonary compliance." (43)
- Standardized use of a cell saver to salvage and readminister shed blood from the operative field and blood remaining in the circuit after CPB has been shown to significantly decrease perioperative donor blood transfusion requirements in children. (48)
- Miniaturization of the circuit is the most effective way of reducing prime volumes, hemodilution, and the blood-surface interface. This is achieved by using roller pumps (vs centrifugal), oxygenators with integrated arterial line filters, smaller internal diameter tubing, and reducing tubing lengths between the pump and patient by stacking pumps vertically on masts of the CPB machine, allowing closer positioning to the patient. (43)(44)(45)(46)(47)
- Although not widely used, several studies have shown the feasibility of using autologous umbilical cord blood to prime a miniaturized CPB circuit or replace perioperative blood loss. (49)(50)

These advances in part or taken together can provide a strategy to reduce or eliminate homologous blood transfusion and donor exposure for many congenital heart surgical patients. These blood reduction management strategies have the added benefit of reducing postoperative edema, circulating inflammatory mediators and activated leukocytes. Although pediatric patients of the Jehovah's Witness faith may have accelerated the pursuit of bloodless pediatric cardiac surgery, all patients benefit from improved cardiac, lung, and renal function, as well as decreased postoperative bleeding and duration of mechanical ventilation observed after using these strategies. (44)(47)

Regional Perfusion During Deep Hypothermic Circulatory Arrest. Deep hypothermic circulatory arrest (DHCA) is a perfusion strategy often used during reconstruction of the aortic arch or repair of total anomalous pulmonary venous return. Selective antegrade cerebral perfusion via the innominate or carotid arteries is a well-established, widely used technique to minimize hypoxic-ischemic injury to the brain during periods of DHCA. Recently, techniques have been described to provide direct selective splanchnic blood flow via antegrade perfusion of the descending aorta or retrograde perfusion of the femoral artery cannulated with a small percutaneous catheter, thereby improving renal and gut perfusion. (51)(52)

Near infrared spectroscopy, which is routinely used in the OR and ICU, provides an estimation of regional oxygen saturations. Near infrared spectroscopy monitoring of the cerebrum and flank (somatic) provides continuous, real-time assessment of the adequacy of perfusion, which is particularly useful during periods of selective regional perfusion under DHCA.

Anticoagulation Management. Within seconds of blood exposure to artificial, nonendothelial surfaces there is rapid activation of coagulation and inflammatory pathways, as well as adsorption of proteins to the surface, leading to a cascade of events that can result in thrombotic and/or hemorrhagic complications. Children with CHD are particularly susceptible to hemostatic derangements on CPB given their immature coagulation systems, antithrombin III deficiency, hemodilution of coagulation factors, platelet hyperreactivity, and prolonged bypass times required to repair complex lesions. Recent strategies to ameliorate the adverse effects of CPB on hemostasis include:

- Increasing use of heparin-coated, bioactive surfaces on CPB tubing and devices
- More precise heparin and protamine management using a commercial hemostasis management system provides a heparin dose response test and point-of-care heparin assay for individualized heparin and protamine management. (53)
- Miniaturizing CPB circuits (as described earlier) to reduce blood-surface interface

Myocardial Protection. The del Nido cardioplegic solution was "developed to induce myocyte depolarization with potassium, a concurrent sodium-channel blockade using lidocaine and calcium antagonism with magnesium." (54) The del Nido solution was specifically designed for children because of their immature myocardium, which is susceptible to edema and highly sensitive to calcium. Advantages of the del Nido solution are its ability to provide appropriate myocardial protection for longer periods with less frequent dosages. It is not unusual for patients to receive a single dose for up to 2 hours of aortic cross-clamping versus every 20 minutes with other solutions. Fewer doses translate into less interruption during the operation and potentially decreased cross-clamp times.

Postoperative Care

Multiple studies have demonstrated improved outcomes and cost savings when treating cohorts of critically ill patients in dedicated specialty units (eg, neurologic, oncologic) versus general ICUs. (55)(56) Over the last several decades, "pediatric cardiac intensive care has emerged as a

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distinct clinical entity to meet the unique and specialized needs of patients with CHD."(57) Concomitantly, there has been a shift toward care of these perioperative patients in specialized units and by staff dedicated exclusively to CHD. Although the concept of a dedicated CICU for postoperative care is intuitively advantageous and justified, its impact on patient outcomes and cost-effectiveness is difficult to measure across hospitals with differing structures, processes, and surgical volumes.

The physical structure or location of a dedicated unit may not be as critical to achieving better outcomes as are other ICU-related factors such as care models (eg, multidisciplinary), availability of personnel, and standardized management protocols, as well as training and education. Having a dedicated, specialized unit and team facilitates *daily multidisciplinary rounds,* enabling collaboration among physicians (surgeon, cardiologist, intensivist) and other clinical disciplines (nursing, respiratory therapy, pharmacy, nutrition support, social work). Family members are encouraged to participate in rounds, promoting communication and transparency. The EASE application (discussed earlier) has become a useful adjunct for families unable to be present for rounds. Most centers managing patients undergoing congenital heart surgery have adopted an intensivist-led team approach, embracing a robust culture of multidisciplinary care and quality improvement. (58)

The practice of *24/7 in-house intensivist coverage* has emerged as one mechanism to address the off-hour needs of these high-risk, high-acuity patients. Multiple studies in adult and pediatric patients have demonstrated the rationale for, and benefits of, 24/7 intensivist coverage including improved outcomes, shorter hospital stays, and overall cost savings as well as improved provider and family satisfaction. (59)(60)(61) When intensivists are available 24/7, the care plan formulated earlier in the day during multidisciplinary rounds is consistently, continuously, and expeditiously followed, without delaying necessary procedures or interventions. Responses to titration of inotropes and sedation as well as weaning of mechanical ventilatory support can be closely monitored. Historically, nursing is more likely to alert the intensivist to concerns or raise questions if the intensivist is in the ICU or nearby. The critical role that an experienced nurse with repetitive exposure to postoperative pediatric cardiac patients plays cannot be overemphasized. Subtle changes in a patient's condition (especially neonates), if left unchecked, can rapidly lead to progressive deterioration with catastrophic effects. Time is of the essence. Rather than relying on a picture of the patient articulated over the phone by the nurse, an in-house intensivist can quickly be at the bedside to assess the patient and initiate change. 24/7 intensivist in-house coverage also improves nursing and other team member satisfaction by reducing their anxiety and stress levels.

Implementation of *standardized management protocols* has been shown to improve outcomes by decreasing hospital-acquired pressure injuries and infections. (62)(63) Some additional examples of the benefits of standardized protocols for postoperative congenital heart surgery patients are:

- Adherence to standardized feeding protocols has been shown to improve weight gain in high-risk neonatal cardiac surgical patients. (64)
- "Implementation of a chest tube removal algorithm for pediatric cardiac surgical patients resulted in decreased chest tube duration and was associated with decreased length of stay and costs without an increase in reinsertions." (65)
- "Implementation of a pediatric comfort algorithm reduced opioid and benzodiazepine dosing, without compromising safety for postoperative pediatric cardiac surgical patients." (66)

Recruitment, retention, and training of nursing staff is critically important to the integrity and stability of the CICU team. A recent study noted that "higher levels of nursing education (Bachelor of Science and higher) and experience (>2 years) are significantly associated with fewer complications after pediatric cardiac operations."(67) Having a dedicated CICU nurse educator is extremely beneficial to facilitate continuing education and engage the team in repetitive simulations of clinical scenarios. (68)

Discharge Planning

Comprehensive discharge planning is critically important to ensure a safe and effective transition to the home. Use of discharge teaching checklists and parent *journey boards* are helpful to facilitate the family discharge teaching process. It is important to engage parents early in their child's admission and provide continuous, repetitive education throughout their hospital stay. Many programs require patients to pass a car seat safety test and parents to complete basic life support training before discharge. Parents may benefit from a 24- to 72-hour rooming-in period before discharge where they are required to independently provide total care for their child. This rooming-in process gives the hospital staff an opportunity to observe how the parents interact with their child and assess their competency in administering medications, feeding, using home equipment, and tending to the child's needs. This is particularly important for high-risk patients (see Outpatient Care section later in this article). Follow-up visit appointments are made with their

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primary care provider, cardiologist, and other specialists as needed. Social workers and discharge planners are essential for coordination and authorization of medications, home monitoring equipment, nursing services, and transportation. Prescriptions can be called in or emailed ahead of time, ensuring that the medications are available and compoundable at the patient's preferred local pharmacy.

Palliative Care

Pediatric palliative care or pediatric advanced care (PAC) has emerged as a critically important component of the multidisciplinary team approach to the care of patients with CHD. Palliative care focuses on the psychological, social, and spiritual needs of children (and their families) with life-threatening or terminal conditions. Palliative care seeks to enhance quality of life for the patient and family through the course of an illness by being sensitive to, and respectful of, the goals, wishes, and values of patients and their families. PAC teams can aid with advance care planning, goal setting, medical decision-making, and bereavement support (if needed) as well as serve as an objective third-party advocate for the patient and family.

Patients with CHD are exposed to significant morbidity and mortality throughout their lifetime. "Prenatal diagnosis offers the opportunity for anticipatory comanagement of patients between PAC and cardiac care teams. This includes support for longitudinal decision making and avoidance of interventions not consistent with family goals, especially in patients born with severe genetic and/or other congenital anomalies." (69)

Outpatient Care

Patients with HLHS or other single ventricle variants following the Norwood stage 1 procedure are a particularly vulnerable group of patients after discharge from the hospital. The combination of a volume-overloaded single right ventricle, inefficient and labile parallel systemic/pulmonary circulation, and cyanosis is a setup for poor weight gain, failure to thrive, and heart failure. These patients are dependent on pulmonary blood flow via either a prosthetic Blalock-Taussig or Sano (right ventricle-to-pulmonary artery) shunt. These shunts are fixed in size, do not grow with the patient, and are prone to stenosis and/or thrombosis. Given their limited cardiopulmonary reserve, common childhood upper respiratory or gastrointestinal infections can be extremely debilitating for these patients. Poor oral intake, vomiting, diarrhea, fever, irritability, and increased work of breathing are poorly tolerated and can quickly lead to dehydration, worsening cyanosis, and cardiac dysfunction. The period between discharge from the hospital after stage 1 palliation and the second stage (eg, Glenn shunt) is commonly referred to as the *interstage period* and typically varies from 3 to 5 months. Single-center interstage mortality rates for infants with HLHS have previously been reported between 10% and 19% and has been a major focus for quality improvement. (70)

One of the most effective quality improvement initiatives of late has been the implementation of comprehensive *home surveillance monitoring (HSM)* programs to coordinate and enhance outpatient care for high-risk patients. This requires a family-centered, multidisciplinary team approach with emphasis on early detection of, and intervention on, signs of physiologic alteration. The main goals of early detection are to prevent growth failure, readmission of patients in extremis, and fatalities. Family involvement and engagement is critical to the success of HSM programs. HSM starts with focused education and training of the parents before the patient is discharged from the hospital. Using home equipment provided to them (digital infant scale, oxygen saturation monitor), parents are taught to obtain and record daily their infant's weight, oxygen saturation, heart rate and enteral intake. They are trained to monitor for specific (red flag) symptoms (70):

- Oxygen saturation less than 75% or greater than 90%
- Any weight loss greater than 30 grams
- Failure to gain at least 20 grams in 3 days
- Enteral intake less than 100 mL/kg per day

The family is instructed to contact the HSM team immediately on detection of any red flag symptoms or changes in their infant's behavior (eg, irritability, increased work of breathing, feeding problems, fever, vomiting, or diarrhea) and are provided with a direct phone number to a dedicated HSM or cardiology team member who is available 24/7 and able to trigger an action plan. HSM nurses should have weekly contact with the family to track the infant's progress, assess family concerns, and reinforce education. Weekly to biweekly clinic visits allow in-depth evaluations by a dedicated, multidisciplinary HSM team (eg, cardiologist, advanced practice nurse, social worker, dietician, speech/feeding specialist, case manager) to coordinate care, assess the patient's progress and optimize nutrition and growth.

Implementation of a comprehensive HSM program has transformed the outcomes for interstage HLHS infants, with some centers achieving 100% interstage survival rates. (71)(72) Since 2008, the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) has identified and disseminated best practices for decreasing interstage mortality. The 60+ NPC-QIC participating sites reduced interstage mortality by 46% (9.5%–5.1%) through implementation of HSM, achieving

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95% interstage survival and 77% satisfactory interstage growth. (73) This is a remarkable example of how collaboration and use of a national data registry can improve health outcomes.

CONCLUSION

Congenital heart surgery is a team sport and depends on an organizational culture that fosters team engagement, collaboration, and commitment to quality, safety, and continuous improvement. It is incumbent upon each congenital heart surgery program to meet or exceed standards established through participation in national databases and collaborative learning groups. Opportunities exist to influence and improve quality of care for congenital heart patients along their entire life timeline, from prenatal diagnosis, through perioperative intervention and outpatient care. With advances in medical and surgical technology, growing numbers of adults are living with CHD (estimated at 1.4 million). Formed in 1998, the Adult Congenital Heart Association is dedicated to improving and extending the lives of millions of patients born with CHD by education, advocacy, and research. (74) One of their primary functions is the accreditation of adult congenital heart disease programs, of which there are currently more than 25 nationwide.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the issues in the organization of perinatal care (eg, regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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Quality Improvement in Congenital Heart Surgery

Timothy W. Pettitt

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1 Preterm Neonate with Persistent Respiratory Distress Despite Interventions

Stephanie Satchell, MD,* Sebastian Welsh, MD*

*Department of Pediatrics, Brooke Army Medical Center, Fort Sam Houston, TX

PRESENTATION

A preterm male neonate is born at 31 weeks of gestation via cesarean section for a category 2 fetal heart tracing. The prenatal history is significant for maternal autosomal dominant polycystic kidney disease (ADPKD). The pregnancy had been complicated by maternal chronic hypertension, preeclampsia with severe features, and significant enlargement with increased echogenicity of fetal kidneys on ultrasonography. Maternal laboratory findings are reassuring and antenatal steroids complete before delivery. At delivery, the neonate has poor respiratory effort, requiring continuous positive airway pressure and is transferred to the NICU. On arrival, he is noted to be in respiratory distress with coarse breath sounds bilaterally, grunting, and significant retractions. Evaluation for infection is initiated and antibiotics started. A chest radiograph is significant for hyperexpansion with bilateral diffuse alveolar and interstitial opacities. He undergoes intubation and receives surfactant twice. Following surfactant administration, he continues to receive mechanical ventilation.

CASE PROGRESSION

He undergoes extubation on day 7 after birth and receives 6 L/min high-flow nasal cannula. He is unable to wean further because of intermittent tachypnea, desaturations, and worsened retractions with weaning. Chest radiography consistently shows diffuse alveolar and interstitial opacities, and the infant has no clinical improvement despite several trials of furosemide, albuterol, budesonide, and fluid restriction (Fig 1). By day 23 after birth, a 3-day course of dexamethasone is tried, which leads to some improvement, allowing the infant to be weaned down to 2.5 L/min nasal canula. Nonetheless, results of radiography and lung examination remain unchanged. Following completion of steroids, his respiratory status worsens, requiring progressively increased respiratory support. Echocardiography shows no signs of persistent pulmonary hypertension. He then starts a trial of ipratropium and repeated systemic steroids without improvement. Chest computed tomography (CT) performed because of lack of clinical improvement shows diffuse ground glass and hazy opacities with scattered intraparenchymal air-filled cysts, regions of intra- and interlobular septal thickening, and linear bandlike atelectasis in the dependent right lower lobe (Fig 2).

AUTHOR DISCLOSURE Drs Satchell and Welsh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

This infant has respiratory distress, examination findings, radiographic findings, and hypoxemia signs that are disproportionate to gestational age. He also received

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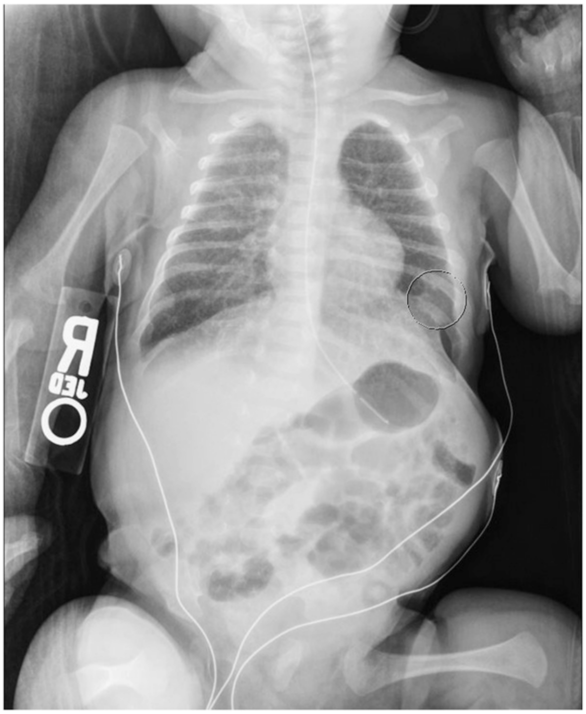

Figure 1. Chest radiograph 23 days after birth showing persistent bilateral diffuse interstitial opacities.

antenatal steroids and surfactant. His respiratory status has not responded to typical treatments for neonatal respiratory distress or infection. This requires an expanded differential diagnosis beyond the common causes of neonatal respiratory distress to include interstitial lung disease (ILD).

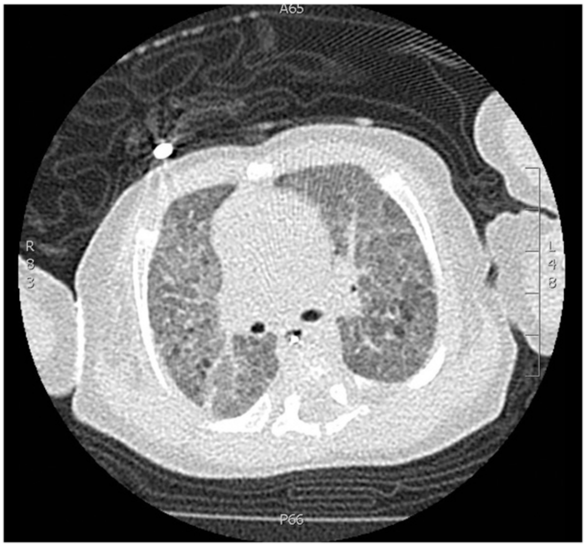

Figure 2. High-resolution chest computed tomography scan 23 days after birth showing diffuse ground glass and hazy opacities with scattered intraparenchymal air-filled cysts, regions of intra- and interlobular septal thickening.

Children's interstitial lung disease (chILD) covers a number of distinct pathologic processes that result in diffuse lung diseases in children. (1) The likelihood of ILD in neonates increases as a result of respiratory distress as gestational age increases. The clinical definition for chILD syndrome requires the presence of at least 3 of the following 4 criteria: respiratory symptoms including cough, rapid breathing, or exercise intolerance; physical signs including crackles, adventitious sounds, digital clubbing, resting tachypnea, or retractions; hypoxemia; and diffuse parenchymal abnormalities on radiography or CT. (1)(2) Once further investigation is deemed warranted, evaluations can involve bronchoscopy with bronchoalveolar lavage, high-resolution CT, genetic testing especially for surfactant dysfunction mutations, and lung biopsy.

Disorders more prevalent in infancy are further subdivided into 5 main categories. These include diffuse developmental disorders, growth abnormalities, pulmonary interstitial glycogenosis (PIG), neuroendocrine cell hyperplasia of infancy (NEHI), and surfactant dysfunction disorders. Diffuse developmental disorders arise early in lung development and are diagnosed on lung biopsy or postmortem tissue because these tend to be universally fatal. (1)(2) Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) is rare and presents early after birth, rapidly requiring lung transplantation. NEHI typically presents in the first year after the newborn period and has diagnostic histologic findings such as bombesin-immunopositive neuroendocrine cells in bronchioles and the interstitium. Surfactant disorders can present throughout infancy but are most common in the neonatal period. They are associated with genetic mutations in *SPB*, *SPC*, and *ABCA3*; treatment often involves transplantation or aggressive long-term ventilation. (1)(2) Choreoathetosis, congenital hypothyroidism, neonatal respiratory distress syndrome (also known as *brain-lung-thyroid syndrome*) is a rare genetic cause of neonatal respiratory distress resulting from a mutation in *NKX2-1*. (2)

PIG is unique to young infants with symptoms soon after birth, with diagnostic histologic findings of increased glycogen-laden mesenchymal cells in the alveolar interstitium. The most common CT findings of PIG are ground glass opacities and cystic lucencies. (3) These findings overlap significantly with those of surfactant disorders, so additional testing is necessary to make the diagnosis. The CT appearance of PIG is distinct from that of NEHI. NEHI has ground glass opacities, predominantly affecting the right middle lobe and lingula, with hyperinflation. Treatment varies dramatically based on clinical severity of disease and comorbid conditions. Some patients have significant response to corticosteroids whereas

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others show no significant improvement. (4) The response to steroids and overall risk/benefit in neonates should be taken into account before prolonged or high-dose steroids are used. Most cases of PIG are self-limited with the condition improving and resolving as the child grows. (4)

The neonate in the current case underwent genetic testing consisting of *FOXF1* (ACDMPV), *NKX2-1 SPB*, *SPC*, *ABCA3*, chromosomal microarray, and whole exome sequencing without pathogenic mutations. With no genetic abnormalities and consistent chest CT findings, the neonate was diagnosed with PIG. His condition gradually improved and he was unresponsive to steroids. His treatment was supportive, with a focus on adequate growth, avoiding lung injury from aspiration, and minimizing infectious insults. He was discharged from the hospital with his parents 106 days after birth. Consistent with PIG, he has had gradual improvement in his work of breathing and resolution of his examination findings.

Lessons for the Clinician

- Interstitial lung disease increases in likelihood as a result of neonatal respiratory distress with increasing gestational age.
- chILD syndrome requires at least 3 of the following 4 criteria: respiratory symptoms, physical signs, hypoxemia, and diffuse parenchymal abnormalities on imaging.
- chILD syndrome can occur without a known cause, developing soon after birth or later in childhood. Index of suspicion for chILD should increase for infants with persistent respiratory concerns despite multiple interventions and disproportionate respiratory distress for gestational age.

DISCLAIMER

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Suggested Readings

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Case 1: Preterm Neonate with Persistent Respiratory Distress Despite Interventions

Stephanie Satchell and Sebastian Welsh

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2 *GATA6* Mutation Responsible for Multiple Congenital Anomalies in 2 Siblings

John Juneau, DO,* Tiffany Wright, MD,† Rodica Turcu, MD†

*Departments of *Pediatrics and †Pediatric Surgery, University of Louisville School of Medicine, Louisville, KY*

PRESENTATION

A white female infant is born at 36 weeks and 6 days to a 32-year-old woman via repeat cesarean delivery. Prenatal fetal ultrasonography identifies truncus arteriosus (TA) and possible left congenital diaphragmatic hernia (CDH). The pregnancy had been complicated by severe intrauterine growth restriction, and the infant is born with a birthweight of 1,580 g (<3rd percentile for gestational age). Physical examination findings at birth are remarkable for small size for gestational age, slightly dysmorphic facial features, pallor, mild cyanosis, mild respiratory distress, grade III/VI systolic murmur, prominent genitalia, and rocker bottom feet. Initial chest radiograph is not clearly diagnostic for CDH and shows abnormal ribs and vertebrae. The radiograph is initially interpreted as a possible eventration of the diaphragm, especially in the clinical setting of low respiratory support requirements (nasal continuous positive airway pressure [CPAP] after delivery). Initial echocardiography shows TA type 1, membranous ventricular septal defect, and atrial septal defect. Serum glucose remains within normal limits during the first 2 days after birth with the administration of dextrose-containing fluids. All additional initial laboratory test results are unremarkable. On the second day after birth, the infant develops hyperglycemia, with serum glucose ranging from 200 to 379 mg/dL (11.1-21.0 mmol/L), requiring intravenous insulin. This finding, in the context of a sibling with a similar clinical presentation, raises the suspicion of neonatal diabetes.

Abdominal ultrasonography shows gallbladder agenesis but no definite pancreatic abnormality. During the first week after birth, the infant improves from a respiratory standpoint and is able to wean off CPAP to room air. However, at age 1 week, her respiratory status worsens, requiring respiratory support escalation. With worsening respiratory symptoms, computed tomography of the chest and abdomen is performed, which shows left CDH with abdominal contents (stomach, spleen, and small intestine) protruding into the left hemithorax, and possible pancreatic agenesis. On day 9 after birth, the infant undergoes surgery for left CDH repair and exploration of the abdominal cavity for congenital abnormalities. Left CDH is confirmed and primarily repaired. The procedure also confirms gallbladder agenesis and pancreatic agenesis. The neonate recovers well after surgery. However, she develops cardiac failure around 3 weeks after birth and receives conservative management with diuretics. Her size and additional anomalies are a relative contraindication for primary TA repair at that time. Around that time, she develops acute direct hyperbilirubinemia, with a peak direct bilirubin of

AUTHOR DISCLOSURE Drs Juneau, Wright, and Turcu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Turcu's current affiliation is Department of Neonatology, Tufts Medical Center, Boston, MA.

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10.6 mg/dL (181 μmol/L). A hepatobiliary scintigraphy scan suggests biliary atresia, and liver biopsy is inconclusive. Genetic testing includes comparative genomic hybridization (CGH), result of which is unremarkable, followed by whole exome sequencing.

The parents of the neonate have had 4 children. Their first child (born 5 years before the neonate) was a late preterm male born with TA type 2, left CDH, and neonatal diabetes. That child underwent surgical repair of his CDH and TA. He was given insulin for his neonatal diabetes. He continued to undergo various inpatient procedures (including tracheostomy and gastrostomy tube placement in addition to the repair of his anomalies) for almost 5 months. He died at age 5 months, a couple of days after being discharged. On autopsy, he was found to have gallbladder agenesis and pancreatic agenesis. Result of CGH performed on that child was unremarkable. A year after his birth, the couple had their second child, who was born without any obvious anomalies. A year before the current neonate, the couple had their third pregnancy, which resulted in fetal death at 24 weeks; no genetic tests were performed.

DISCUSSION

At about 1 month of age, the neonate was transferred to another facility for a second opinion per parental request. She was too unstable for TA repair, so she underwent palliative pulmonary artery banding. She underwent postoperative decompensation, requiring extracorporeal membrane oxygenation and the family decided to withdraw support.

The neonate described here had an unusual association of multiple congenital abnormalities, very similar to her sibling, so a genetic cause was suspected. Initially her CGH result was unremarkable (like her brother's), but whole genome sequencing was performed and was positive for monoalleic *GATA6* mutation.

GATA6 binding protein is essential for the endodermal development of the heart, lungs, and gut.

The gene coding for this protein is found at Ch18q11.12. *GATA6* plays a crucial role in the organogenesis of multiple organ systems. Defects in the gene cause downregulation of essential endodermal markers, including Hnf4a, Hnf3b, Afp, and GATA4, and inhibit endodermal differentiation. (1) To date, around 34 known mutations of *GATA6* with extensive phenotypic variability have been described in the literature. (2) *GATA6* mutations have been known to cause pancreatic agenesis, with subsequent neonatal diabetes and congenital heart defects in as many as 93% to 100% of cases. (3)(4) It has been found to play a crucial role in semaphorin 3C (SEMA3C) and plexin A2 (PLXNA2) signaling, both involved in normal heart development. Its mutations result in various congenital heart defects, most commonly outflow tract defects such as TA. (5) Recently *GATA6* mutations have surpassed *PDX1* and *PTF1A* mutations as the most common cause for pancreatic agenesis (>50% of the known 77 cases). (4)(6)(7)(8)(9)

GATA6 mutations are associated with a spectrum of other anomalies including hepatobiliary defects (gallbladder agenesis, biliary atresia), gut abnormalities (malrotations, hernias), hypothyroidism, neurocognitive defects, CDH, and pericardium defects. (2)(7) CDH is a recent addition to the known *GATA6* congenital associations. A 2014 study concluded that CDH in the presence of congenital heart abnormalities should be prioritized for screening for *GATA6* mutations given how rarely the 2 anomalies are seen together. (2)

Overall, *GATA6* has variable phenotypic presentations and severity of symptoms. In the presence of 1 of the anomalies commonly associated with *GATA6*, it is important to evaluate all other possible abnormalities. Even more so, it is important to have a high level of suspicion for the mutation when congenital heart disease is found in the presence of neonatal diabetes mellitus and/or CDH. It is important to emphasize that the *GATA6* mutation is not identified on routine karyotype or CGH testing, so whole exome sequencing should be performed if the suspicion exists. Even though *GATA6* mutations are very rare, the effects can be severe, as seen in these siblings. Early identification of these conditions could be pivotal in early management and improved outcomes.

Lessons for the Clinician

- In a case of a neonate with prenatally or postnatally identified congenital anomalies, it is important to evaluate for associated anomalies, because early identification allows for early and adequate treatment.
- Some genetic mutations are not identified on karyotype or CGH testing, so whole exome sequencing should be performed when suspicion exists.
- *GATA6* mutation has emerged as the number 1 cause of pancreatic agenesis.
- One should have a high level of suspicion for the *GATA6* mutation when congenital heart anomalies are associated with neonatal diabetes mellitus as well as CDH.

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American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Formulate a differential diagnosis for a cyanotic neonate.
- Know the causes, including genetic disorders and other clinical conditions, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the modes of inheritance of various inherited and genetic disorders of the GI tract.
- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.
- Recognize the clinical features and possible associated defects of a cyanotic neonate.

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Case 2: GATA6 Mutation Responsible for Multiple Congenital Anomalies in 2 Siblings

John Juneau, Tiffany Wright and Rodica Turcu

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3 A Newborn with a Mass on the Right Ventricle

Jorge Martin Lopez Da Re, MD*

**Division of Neonatology, Department of Pediatrics, Adventhealth, Ocala, FL*

PRESENTATION

A male neonate is born at 36 2/7 weeks via vaginal delivery at a level 2 nursery. The mother is a 34-year-old, gravida 8, para 4, aborta 3 woman.

The maternal history is remarkable for chronic hypertension that was treated with labetalol and amlodipine; hypothyroidism that was treated with levothyroxine; and obesity and gestational diabetes that were controlled with diet. Maternal laboratory findings are as follows: human immunodeficiency virus, negative; rapid plasma reagin, nonreactive; hepatitis B, negative; group B *Streptococcus,* negative; blood type, O positive; and antibodies, negative. The mother has not received any medication at the time of delivery. The neonate is born via cesarean section for nonreassuring fetal heart tracing and clear amniotic fluids.

Anthropometric measurements at birth are as follows: weight, 2,740 g (45th percentile); head circumference, 34 cm (77th percentile); length, 45.5 cm (20th percentile); growth status: appropriate for gestational age; Apgar scores, 7 and 8 at 1 and 5 minutes, respectively. The neonate requires positive pressure ventilation for 1 minute after delivery.

On admission to the nursery, the neonate exhibits signs of mild respiratory distress and tachypnea, and is placed on continuous positive airway pressure (CPAP) of 6 cm H_2O with a fraction of inspired oxygen (FIO_2) of 50%; chest radiograph (Fig 1) shows mild ground glass appearance. Because of his worsening respiratory status, the neonate undergoes intubation and is administered surfactant. A few minutes after surfactant administration, the infant's condition suddenly deteriorates, requiring an increase in FIO_2 to 100%. Although the neonate receives maximal ventilator and oxygen support, his oxygen saturation remains under 80%. The presence of a pneumothorax prompts the placement of a left chest tube. He is transferred to a level IV NICU for further management of his condition. At admission, a diagnosis of severe respiratory distress, right pneumothorax, and persistent pulmonary hypertension of the newborn is rendered.

DISCUSSION

On admission, the infant was placed on high-frequency jet ventilation with peak inspiratory pressure (PIP) 40 mm Hg, positive end-expiratory pressure (PEEP) 10 mm Hg, rate of 360 BPM, an FIO_2 of 100%, and inhaled nitric oxide at 20 ppm. A cardiothoracic surgeon was consulted for potential extracorporeal membrane oxygenation.

Maternal and infant platelets were normal on admission. A complete blood cell count 12 hours later showed severe thrombocytopenia (15,000/μL [150×10^9/L]); coagulation profile and liver function tests were normal for age; and

AUTHOR DISCLOSURE Dr Lopez Da Re has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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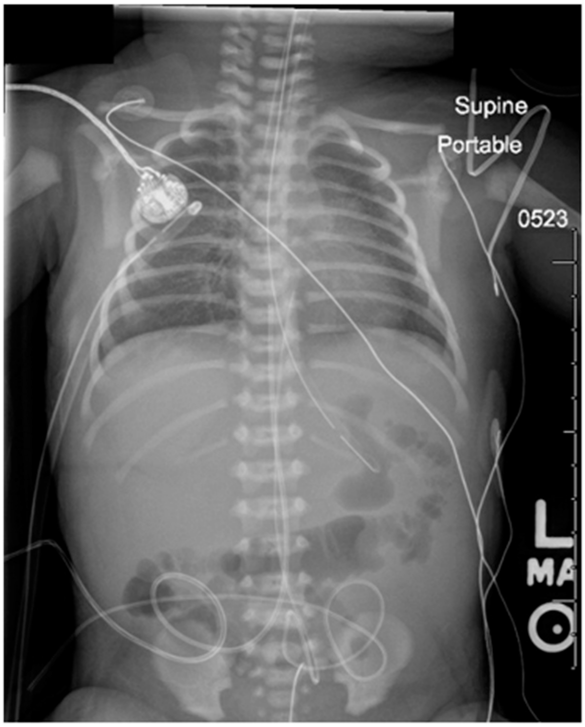

Figure 1. Chest radiography showing mild ground glass appearance.

brain ultrasonography findings were normal. Because of severe respiratory failure and absence of response to maximal respiratory support, echocardiography was requested, which showed 2 masses on the anterior and septal leaflets of the tricuspid valve and pulmonary hypertension with supra-systemic right ventricular pressure and septal bowing (Fig 2). A magnetic resonance imaging of the brain (Fig 3) showed a large area involving encephalomalacia in the posterior right cerebral hemisphere, possibly related to a prior infarction.

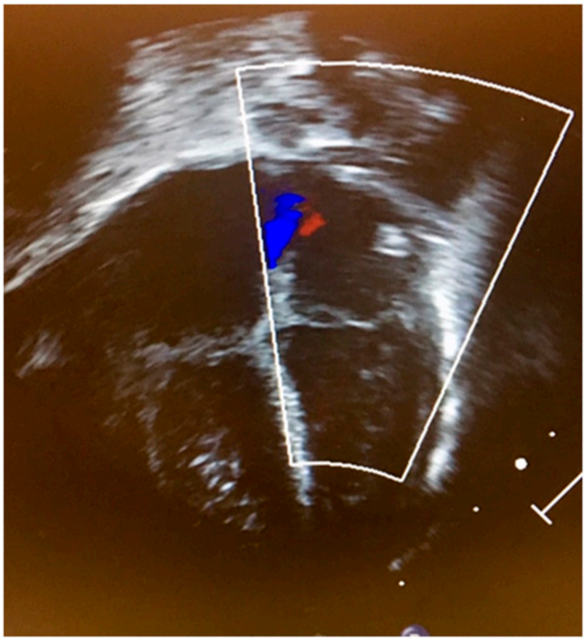

Figure 2. Echocardiogram showing 2 masses on the anterior and septal leaflets of the tricuspid valve and pulmonary hypertension with supra-systemic right ventricular pressure and septal bowing.

Echogenic material from the umbilical line/portal veins (Fig 4) was seen along the course of the umbilical venous line, probably reflecting thrombus. No flow could be elicited within the left portal vein. In addition, arterial flow was prominent in the proximity of the left portal vein, which was likely compensatory. The right and main portal veins were widely patent.

Hospital Course

The neonate was given anticoagulation treatment, and the thrombi started to decrease in size at 72 hours and pulmonary pressures dropped as well. We suspected pulmonary vein thrombosis caused by a decrease of the flow, though echocardiography was not able to show thrombosis. We were not able to perform cardiac catheterization at the time because of the cardiorespiratory compromise first and then the risk of bleeding with anticoagulation treatment. Inhaled nitric oxide was weaned after 48 hours, FIO$_2$ was weaned to 21% on day 5, and the infant underwent extubation on day 8 to receiving nasal CPAP. Feeding started on day 7. The infant was discharged after 2 weeks with subcutaneous low-molecular-weight enoxaparin; he received full feedings by mouth and was stable in room air.

Maternal laboratory findings, placental pathology, and infant sepsis screening were all negative. Testing of the mother for protein C and S deficiency showed normal results.

The Condition

Hyperhomocysteinemia, methylenetetrahydrofolate reductase (*MTHFR*) heterozygote mutation, associated with low protein C and S, severe respiratory distress syndrome, severe pulmonary hypertension, pneumothorax, hypotension, clinical sepsis, metabolic and respiratory acidosis, and placement of central catheters potentially contributed to this overwhelming presentation of multiple venous and arterial thrombosis (cardiac, portal vein, right nonocclusive venous thrombosis in the bilateral sigmoid sinuses of the brain, and encephalomalacia).

Carriers of *MTHFR* C677T/ A1298C are not at increased risk for thrombosis in the absence of hyperhomocysteinemia. (1)(2)(3)(4)(5) However, in the presence of other risk factors (perinatal asphyxia, septicemia, dehydration, and maternal diabetes), venous and arterial thrombosis can occur. (6) The infant described here had mild elevated homocysteine and the *MTHFR* heterozygote

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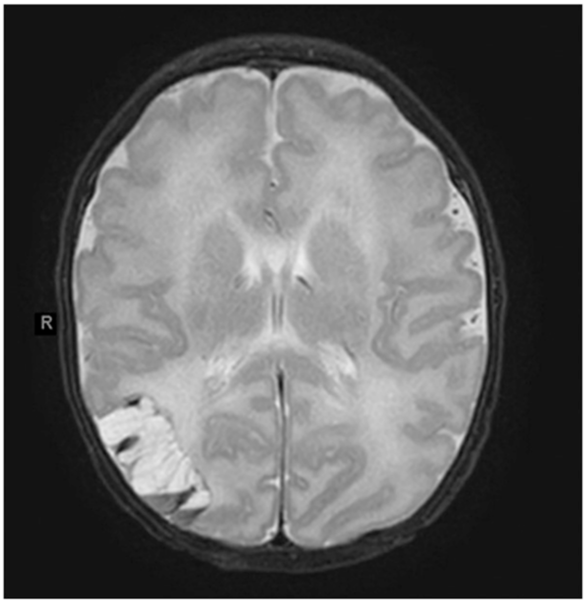

Figure 3. Magnetic resonance imaging of the brain showing a large area of encephalomalacia in the posterior right cerebral hemisphere, possibly related to a prior infarction.

mutation associated with other risk factors for thrombophilia. The single most important risk factor for the development of arterial or venous thrombosis events is an indwelling central catheter, with thrombi commonly involving large vessels. These events are unusual, but their occurrence increases in the presence of coagulation and other risk factors.

At birth, the hematologic system is not fully developed compared with adults. (6) The neonate described here presented with a relatively normal complete blood cell count, and in less than 12 hours, developed severe thrombocytopenia. Coagulation studies were within normal range at that time, with the prothrombin time being 15 seconds, partial thromboplastin time 40 seconds, and fibrinogen 150 mg/dL (4.4 μmol/L). Protein C and S activity was low (6% [normal 15%–50%] and 30% [normal ≥ 50%], respectively). The *MTHFR* C677T/ A1298C heterozygous gene mutation on a single allele was detected (heterozygous mutant), and homocysteine level was in the lower limit (6 μmol/L or 0.6 mg/L) (normal $<$5 μmol/L or 0.5 mg/L). Other tests included β_2-glycoprotein 1 immunoglobulin (Ig) G/IgM (negative), cardiolipin IgG/IgM (negative), factor VIII activity assay (WNL), lupus anticoagulant, protein C antigen 12% (mildly low), protein S antigen 43% (acceptable), and antithrombin III elevated (50 mg/dL [500 mg/L] normal value $>$ 30 mg/dL or $>$ 300 mg/L).

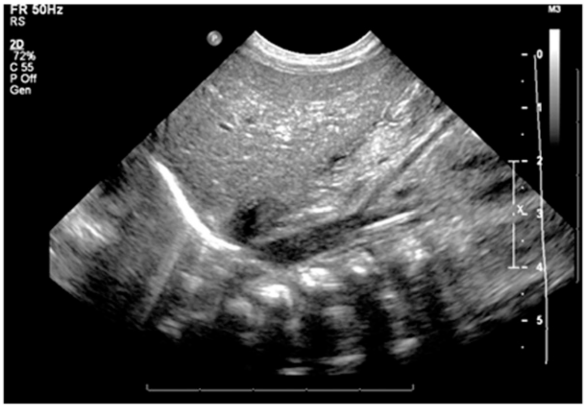

Figure 4. Echogenic material from the umbilical line/portal veins was seen along the course of the umbilical venous line, probably reflecting thrombus.

Compared with adults, procoagulant proteins, particularly the vitamin K–dependent and contact factors, are reduced in the term neonate. (7) Although α_2-macroglobulin is significantly increased at birth, inhibitors of coagulation, antithrombin, heparin cofactor II, protein C, and protein S are reduced. (7) The fibrinolytic system also appears different, with plasminogen concentrations around 50% of adult values. (8) Preterm infants have more pronounced variation in these factors. (9)

Management

The infant was given anticoagulation treatment at 48 hours after birth, and his venous and arterial thrombi started to decrease in size with improvement in his clinical condition. Enoxaparin failed to reach the target level of anticoagulation, thus requiring heparin infusion. We theorized that low-molecular-weight heparin absorption was decreased because of severe fluid retention and anasarca. Heparin treatment was associated with mild asymptomatic thrombocytopenia.

Echocardiography and abdominal ultrasonography showed a decrease in the size of the thrombi and improvement and resolution of pulmonary hypertension. On discharge, the patient was switched to enoxaparin, with adequate anti–factor X.

Lessons for the Clinician

- In the context of a critically ill neonate, central catheter placement can be associated with deep venous and arterial thrombosis.
- The presence of a thrombus in a sick neonate should trigger further hematologic evaluation and consultation.
- Management should include heparin infusion with anti–factor X levels within target goals.
- Multidisciplinary management with the inclusion of a hematologist and geneticist should be considered in cases with an abnormal coagulation profile and multiple thrombi.

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- Know the inheritance patterns of the common coagulation factor deficiencies.
- Know the causes and pathophysiology of congenital and acquired thrombotic disorders.
- Know the causes and pathophysiology of congenital defects in hemostasis.
- Know the clinical manifestations, laboratory findings, and management of congenital defects in hemostasis.
- Know the pathogenesis and complications of catheter related thrombi including umbilical arterial and central venous catheters.

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Early Fetal Growth Restriction

Rosibel Hernandez Castro, MD, MPH,*† Melissa Spiel, DO*†
*Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA
†Department of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston, MA

ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

AUTHOR DISCLOSURE Drs Hernandez Castro and Spiel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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TABLE. **Arterial Umbilical Cord Gas Values**

	pH	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤–10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤–10
Metabolic acidosis	<7.20	<60	Variable	≥–10
Mixed acidosis	<7.20	>60	Variable	≥–10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable
Minimal: Amplitude range is greater than undetectable to 5 beats/min
Moderate: Amplitude range is 6–25 beats/min
Marked: Amplitude range is >25 beats/min

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
    - Normal: ≤5 contractions in 10 minutes
    - Tachysystole: >5 contractions in 10 minutes

INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

– Baseline rate: 110 to 160 beats/min
– Baseline FHR variability: Moderate
– Late or variable decelerations: Absent
– Early decelerations: Present or absent

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- Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

  - Absent variability with any of the following:
    - ■ Recurrent late decelerations
    - ■ Recurrent variable decelerations
    - ■ Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008; 112:661-666, and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

CASE PRESENTATION

A 40-year-old, gravida 2, para 0-0-1-0 woman with a spontaneous dichorionic diamniotic twin pregnancy had 1 fetal death in the first trimester, and was currently receiving growth surveillance. Ultrasonography for growth was performed at 26 weeks and 6 days' gestational age. Her pregnancy was dated by her last menstrual period and consistent with the first-trimester ultrasonographic findings. Her prenatal course was otherwise uncomplicated with a low risk assessment finding, negative cystic fibrosis and spinal muscular atrophy screening, and reassuring fetal anatomic survey of the surviving twin. She had declined diagnostic testing for aneuploidy. At late second-trimester ultrasonography, the fetus was identified to have growth restriction, with measurements that were consistent with the 5th percentile for gestational age. Umbilical artery (UA) Doppler measurements were normal for gestational age. She continued outpatient surveillance of fetal growth. Her obstetrical history was notable for a first-trimester spontaneous abortion of twins and subsequent dilation and curettage.

CASE PROGRESSION

The patient was referred to a tertiary care center and underwent ultrasonography at 27 weeks and 2 days' gestational age. At that time, fetal growth restriction was confirmed and consistent with the 5th percentile for gestational age. However, additional findings included echogenic bowel, a wide cavum septum pellucidum, subjectively low amniotic fluid, and reversed end-diastolic flow on UA Doppler examination. Given the severe growth restriction and early gestational age, inpatient admission was recommended. She was counseled about the echogenic bowel and opted to have serum infectious screening for cytomegalovirus and toxoplasmosis (both tests were later found to be negative). She was counseled again about the diagnostic capabilities of amniocentesis not only for aneuploidy, but for infectious etiologies and cystic fibrosis evaluation. The patient declined this testing.

She was admitted to the hospital at 27 2/7 weeks' gestational age for monitoring and was evaluated for preeclampsia. She had multiple presenting blood pressure measurements that were elevated but nonsevere (<160/110 mm Hg). On admission, the FHR was monitored. A representation of the fetal heart tracing at this time is displayed in Fig 1. Because of concern for a possible preterm delivery, a betamethasone course was initiated. She met with neonatology for counseling. Her group B *Streptococcus* status was collected on admission.

Interpretation of Fig 1:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: Acontractile
- Interpretation: Nonreactive but appropriate for gestational age

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- Differential diagnosis: Appropriate for gestational age, placental insufficiency in the setting of preeclampsia
- Action: Expectant management with continuous fetal monitoring was recommended; first dose of betamethasone was administered for concern for preterm delivery

To further evaluate for possible preeclampsia, serum laboratory values, including serum creatinine, liver function tests, complete blood cell count, and a urine protein-creatinine ratio, were measured. The analysis revealed normal preeclampsia laboratory results with the exception of a urine protein-creatinine ratio of 0.4, consistent with a diagnosis of preeclampsia. With fetal growth restriction and abnormal UA Doppler findings that showed reversed end-diastolic flow, she met the criteria for preeclampsia with severe features. (1) Given that she had not yet completed her betamethasone course, observation and external fetal monitoring was continued, as shown in Fig 2.

Interpretation of Fig 2:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: Variable deceleration
- Periodic patterns: None
- Uterine contractions: Acontractile
- Interpretation: Concerning for placental insufficiency or cord compression
- Differential diagnosis: Uteroplacental insufficiency (from preeclampsia, concealed abruption, or other entity) or cord compression (in the setting of subjectively low amniotic fluid)
- Action: Maternal repositioning to left lateral position to allow for ideal uterine blood flow and to alleviate cord compression if present. After this adjustment, moderate variability and accelerations were seen, and thus, the decision was made to manage expectantly. The NICU was also notified

She was counseled about the possibility of delivery before completing the betamethasone course if the fetal heart tracing showed persistent evidence of fetal distress. Treatment with magnesium sulfate was initiated for fetal neuroprotection and seizure prophylaxis in the setting of evolving preeclampsia. The following day, the patient received the second dose of betamethasone. Repeat ultrasonography confirmed persistent reversed end-diastolic flow on UA Doppler examination. External fetal monitoring was continued with a representative strip shown in Fig 3.

Interpretation of Fig 3:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic patterns: Late decelerations
- Periodic patterns: None
- Uterine contractions: Irritable
- Interpretation: Concern for uteroplacental insufficiency
- Differential diagnoses: Uteroplacental insufficiency from maternal positioning, maternal fluid status, or maternal or fetal condition
- Action: The patient was counseled about the likely need for delivery, possibly before completion of the betamethasone course, given the fetal testing result

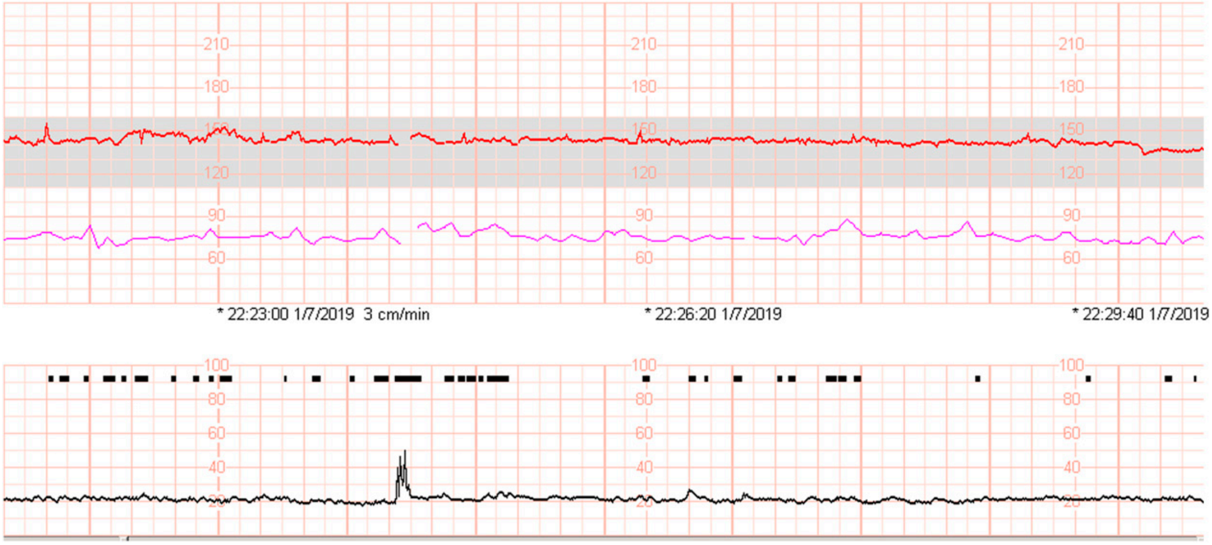

Figure 1. External fetal monitoring strip 1.

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Because there were periods of minimal FHR variability, spontaneous variables, and late decelerations in the setting of fetal growth restriction, reversed end-diastolic UA Doppler flow, oligohydramnios and preeclampsia, the recommendation for delivery and mode of delivery was reviewed with the family. The discussion included the maternal risk of cesarean delivery as it relates to future reproductive health, including the possibility of a classical cesarean delivery and risk of abnormal placentation in future pregnancies, as well as the overall morbidity of general abdominal surgery. Induction of labor was also discussed with the goal of a vaginal delivery, including possible oxytocin stimulation test and the likelihood of fetal intolerance to labor in the setting of fetal growth restriction and spontaneous decelerations before labor induction. The risk for stillbirth with prolonged expectant management was also discussed. The patient opted for delivery via cesarean section after the betamethasone course was complete (ie, 24 hours after the second betamethasone dose).

OUTCOME

A primary low transverse cesarean delivery of a female neonate at 27 weeks and 4 days' gestational age was uncomplicated. The newborn was transferred to the awaiting neonatologist's care after 30-second timed cord clamping. She emerged active, with cyanosis and increased work of breathing. She initially required positive pressure ventilation and was then transitioned to continuous positive airway pressure. Her Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. In the NICU, the neonate underwent intubation for increased work of breathing and was given surfactant. Her birthweight was 470 g (2nd percentile).

The neonate's NICU course was complicated by methicillin-resistant *Staphylococcus aureus* pneumonia at 19 days of age requiring reintubation and support with pressors and infusion of blood products. She received a prolonged course of antibiotics. She underwent extubation and was transitioned to nasal cannula. She was discharged from the hospital after approximately 120 days in the NICU on room air.

Placental pathology revealed a placental weight of 77 g (<3rd percentile for gestational age), along with decidual vasculopathy, chorionic villi with markedly accelerated maturity, and extensive placental infarction, consistent with maternal vascular malperfusion.

The maternal hypertensive disease resolved without the need for additional therapy. After delivery, laboratory testing was performed for an antiphospholipid antibody syndrome given the severe fetal growth restriction and preeclampsia at a very premature gestation. Result of this initial testing was positive for lupus anticoagulant, β_2-glycoprotein, and anticardiolipin antibodies. Follow-up laboratory assessment was recommended, and the diagnosis of antiphospholipid antibody syndrome was confirmed. The patient was counseled about the impact on future pregnancies and the likely need for aspirin and prophylactic anticoagulation. She was counseled that antiphospholipid antibody syndrome is a systemic autoimmune disease characterized by thromboembolism and/or pregnancy complications in the presence of persistent antibody expression. She was also counseled about

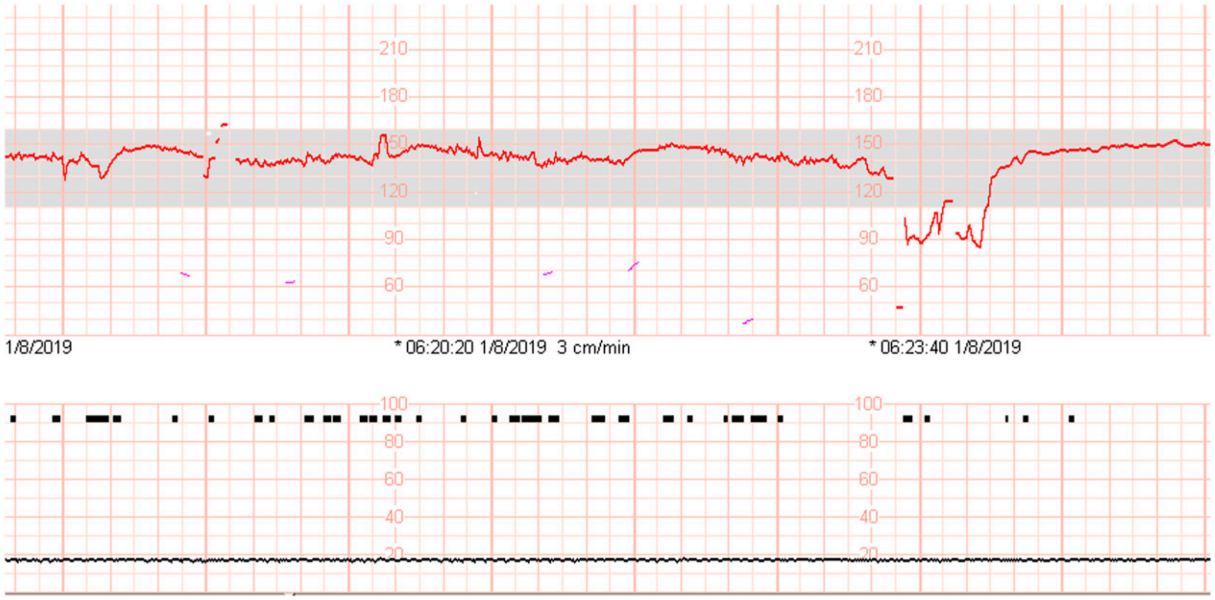

Figure 2. External fetal monitoring strip 2.

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long-term thromboembolism risks and the risk of developing systemic lupus erythematosus. She was referred to a vascular medicine specialist, who continues to follow her for this diagnosis.

DISCUSSION

Fetal growth restriction is typically defined as an estimated fetal weight less than the 10th percentile for gestational age. (2) The etiology of fetal growth restriction can be characterized as fetal, maternal, or placental. (2) Screening for fetal growth restriction involves measurement of fundal height between 24 and 38 weeks of gestation, with a 96% specificity in detecting fetal growth restriction. (2) Ultrasonography can also be used in women whose fundal measurements may be inaccurate because of comorbidities such as obesity or fibroids, as well as those with maternal conditions known to have an increased risk of fetal growth restriction. (2) Such maternal conditions include hypertensive disorders in pregnancy, diabetes mellitus, chronic kidney disease, lupus, antiphospholipid antibody syndrome, sickle cell disease, and substance use. (3) To calculate an estimated weight, the biparietal diameter, head circumference, and abdominal circumference as well as femur length are measured with fetal ultrasonography. (3)

Fetal growth restriction has been associated with an increased risk of intrauterine death, with an approximate risk of 1.5%, about twice the rate of fetuses with normal weights. (2) Neonatal morbidity and death are also associated with severe fetal growth restriction and can be associated with cognitive delay in early infancy. (4) Pregnancies associated with abnormalities in Doppler waveforms, specifically absent end-diastolic UA flow or reversed end-diastolic UA flow, have a higher risk of fetal death or neonatal morbidities. (2)

UA Doppler ultrasonography is a noninvasive assessment of the fetal circulation. (5) Placental perfusion can be assessed with Doppler ultrasonography by measuring blood velocity, direction of flow, volume of flow, and impedance or resistance to flow within the UAs. (4) In normal pregnancies, low impedance allows for forward flow in the fetal cardiac circulation. (2)(4) However, if the pregnancy is complicated by uteroplacental insufficiency, such as with a placental infarction, a decrease in end-diastolic UA flow is observed, which could ultimately become absent or reversed. (4)

In pregnancies with placental insufficiency, determined by fetal findings such as fetal growth restriction and oligohydramnios, UA Doppler surveillance can improve fetal morbidity and decrease the rate of stillbirth by assessing fetal hemodynamics and fetal well-being. (2)(4)(5) In pregnancies complicated by fetal growth restriction, the use of UA Doppler ultrasonography to assess fetal well-being has been shown to reduce fetal death by as much as 29% and has not been shown to increase avoidable interventions. (2)(4) UA Doppler assessment, along with antenatal fetal testing, has been shown to significantly improve fetal and neonatal outcomes by allowing for early intervention in women at high risk for uteroplacental insufficiency. (6)(7)(8)

The Society of Maternal-Fetal Medicine has published guidelines for the management of a fetus with fetal growth restriction and abnormal UA Doppler flow, (4) but does not delineate the management of comorbid conditions (eg, diabetes, preeclampsia, lupus, and twin death), some of which were seen in our case. In isolation, reversed end-diastolic UA Doppler flow in pregnancies with fetal growth restriction should prompt delivery around 32 weeks' gestation. (4) However, the American College of Obstetricians and Gynecologists guidelines for the management of hypertension in pregnancy

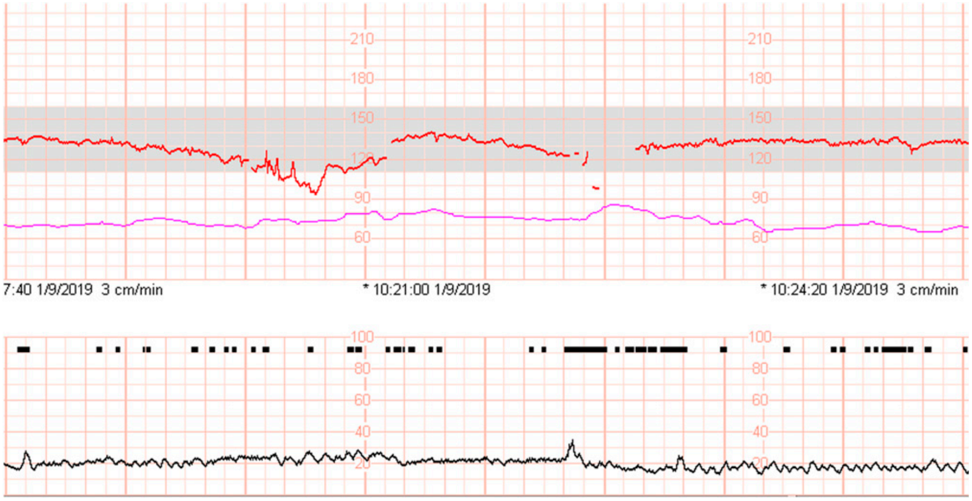

Figure 3. External fetal monitoring strip 3.

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suggest that concurrent fetal growth restriction with reversed end-diastolic UA Doppler flow should prompt delivery when the betamethasone course is complete. (2) In our patient's case, spontaneous fetal decelerations also supported delivery and avoidance of expectant management.

The use of UA Doppler ultrasonography in our case helped to guide management decisions, because this patient's preeclampsia otherwise appeared less severe. The presence of spontaneous decelerations also argues in favor of a suboptimal intrauterine environment. In addition, placental pathology was consistent with placental insufficiency as evidenced by the large infarction, accelerated maturation, and decidual vasculopathy. The early-onset placental insufficiency along with the large placental infarction prompted the decision to evaluate our patient for antiphospholipid antibody syndrome, both to prognosticate future pregnancy outcomes and ideally improve them.

Preeclampsia has been associated with antiphosphlipid antibody syndrome, especially with severe features and presentation at a gestational age less than 34 weeks. (9) Antiphospholipid antibodies have been seen more commonly in women with fetal growth restriction and preeclampsia, (10) similar to our patient. However, the clinical applications of this information are still unclear, and therefore screening is insufficiently supported by evidence of improved outcomes. (9) Further, the optimal treatment for women with antiphospholipid syndrome without a preceding thrombotic event has not been well-established. (9) However, expert consensus suggests clinical surveillance, prophylactic heparin, and low-dose aspirin during pregnancy and the postpartum period.

The use of noninvasive fetal assessment, such as UA Doppler flow, has aided in the management of fetal growth restriction in the setting of prematurity. It allows providers to obtain objective measures to better counsel patients on the possible neonatal and maternal comorbidities associated with expectant management versus delivery, as illustrated in our case. Also, unlike external fetal monitoring, which has limited evidence to support its use to improve outcomes, use of UA Doppler flow has been proven to improve outcomes. When appropriately used, UA Doppler measurements have led to a significant reduction in neonatal comorbidities, such as cognitive delays and stillbirth. (2)(4) Our patient's hospital course was guided by assessment of fetal well-being combined with the use of UA Doppler ultrasonography and external fetal monitoring. The use of both testing modalities facilitated timely interventions and proper counseling by both the obstetrician and neonatologist.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of maternal immunologic diseases and their management.
- Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow measurements, in assessment of fetal conditions and well-being.
- Understand the rationale, interpretation, and limitations of maternal detection of fetal movement, of the biophysical profile, the non-stress test, and the contraction stress test as means of assessing fetal well-being.

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Early Fetal Growth Restriction

Rosibel Hernandez Castro and Melissa Spiel

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Neonate with Hanging Facial Mass

Ekansh Agarwal, MBBS*
*Neonatal Intensive Care Unit, Department of Pediatrics, Kasturba Hospital, Kasturba Medical College, MAHE, Manipal, Karnataka, India

THE CASE

A full-term male newborn was evaluated 1 day after birth for a preauricular skin tag and a 1.5×1.5–cm mass with a long thin pedicle, with its base at the right cheek (Fig).

PRENATAL AND BIRTH HISTORIES

- Born to a 25-year-old, gravida 3, para 2 woman at 40 weeks of gestation.
- Maternal history of hypothyroidism treated with oral thyroxine (50 μg).
- Two older siblings are healthy; no history of similar lesions in the family.
- Pregnancy complicated by vaginal bleeding at 29 weeks of gestation, 2 doses of dexamethasone administered in view of preterm labor.
- Ultrasonography performed at 33 weeks of gestation was normal and fetal growth scans were normal.
- Estimated gestational age: 40 weeks.
- Emergency cesarean section for fetal distress and nonprogression of labor.
- Prenatal maternal laboratory findings: Hepatitis B surface antigen negative, group B *Streptococcus* not known, Rh-negative (received anti-D immunoglobulin).
- Apgar scores: 9 and 9 at 1 and 5 minutes, respectively. Infant cried immediately after birth and routine neonatal resuscitation was performed.

PRESENTATION

At birth, the infant was noted to have a small mass with a thin long pedicle, with its base at the right cheek (Fig). The infant was otherwise asymptomatic and required no active investigation or intervention. The mass was firm without any evidence of tenderness, pulsation, or fluctuation. No other gross anomalies were detected on examination.

PROGRESSION

Vital Signs

- Heart rate: 152 beats/min
- Respiratory rate: 48 breaths/min
- Oxygen saturation: 100% (in room air)
- Temperature: 98.6°F (37.0°C)

Physical Examination

- Birthweight: 2,380 g (<10th percentile), length: 47 cm (<10th percentile), head circumference: 34.5 cm (between 25th and 50th percentile).
- Skin: No icterus, preauricular skin tag, skin tag with a thin long pedicle hanging, with a base at the right cheek, measuring 1.5×1.5 cm.

AUTHOR DISCLOSURE Dr Agarwal has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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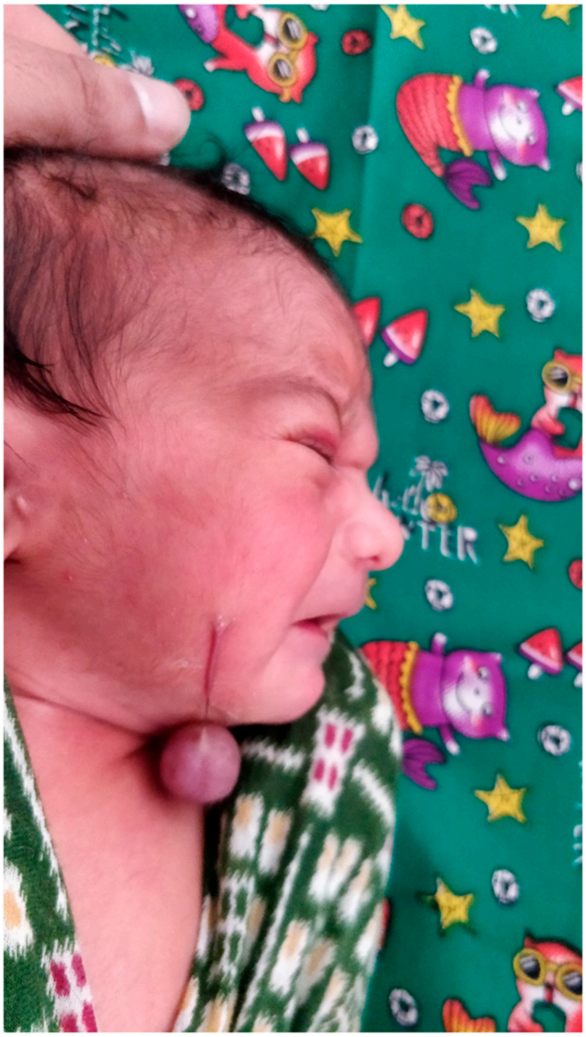

Figure. Neonate with facial mass.

- Head: Normocephalic, open flat fontanelles, anterior fontanelle 2×2 cm, symmetrical facies, patent nares.
- Oral cavity: Pink mucosae, intact palate, no lymphadenopathy, normal sucking and rooting reflex.
- Respiratory system: Bilateral air entry equal, normal vesicular breath sounds, no added sounds.
- Cardiovascular system: S1 and S2 heard, no murmur or gallop.
- Abdomen examination: Soft, nontender, no organomegaly.
- Genitourinary system: Normal male genitalia, bilateral descended testis, patent anus.
- Central nervous system: Active, alert, symmetric Moro reflex, normal tone, reflexes normal.

Laboratory Studies

- Hearing evaluation conducted as part of routine newborn screening was suggestive of normal outer hair cell functioning bilaterally.

Imaging Studies

- Ultrasonography of the mass: No blood vessels detected.
- Ultrasonography of the abdomen: No abnormality detected in the abdomen and pelvis; no obvious renal anomalies detected.

Infant roomed in with the mother and breastfeeding was established. Pediatric surgery consultation was sought. After obtaining informed written consent, the mass along with the pedicle was excised aseptically and the specimen sent for histopathologic examination.

DIFFERENTIAL DIAGNOSIS

- Dermoid
- Fibroepithelial polyp
- Hemangioma
- Teratoid

ACTUAL DIAGNOSIS

The infant was clinically stable and discharged at 7 days of age. Pathologic examination characterized the specimen as single nodular tissue bit, along with the attached portion of skin weighing 2 g and measuring 1.5×1.5×1 cm. On cut section, serous fluid was obtained. Microscopic examination showed polypoidal tissue lined by keratinizing stratified squamous epithelium, subepithelium showing fibrocollagenous tissue, adnexal structures, and blood vessels. Adjacent tissue showed unremarkable skin with epidermis and dermis. These findings were consistent with a diagnosis of fibroepithelial polyp.

What the Experts Say

Fibroepithelial polyp is considered a pseudotumor. Its etiology is largely unknown. Most commonly it is a benign lesion. Studies suggest that the most common sites for fibroepithelial polyp in the head and neck are in the oropharynx, tongue, and skin. (1)

Almost all reported cases of fibroepithelial polyps have been benign, with no recurrence after excision. Some reported cases include fibroepithelial polyp of vagina, which in itself is a rare entity and is usually benign in nature, (2) fibroepithelial polyp of the external auditory canal, (1) and urethral polyp in the neonate. (3).

Even in the current case, the neonate had a preauricular skin tag and mass with a long thin pedicle that was a fibroepithelial polyp of the skin and was benign in nature.

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Skin tags, especially those that are preauricular, may be associated with renal anomalies and hearing impairment, but the incidence of these is very low. Hence, routine renal and hearing evaluation may not be needed in every case. In a study by Yezdan Firat, the prevalence of renal abnormality was found to be 2.7% and hearing impairment was 2.7%. These abnormalities were not seen together in any of those patients. (4)

A dermoid is a cystic lesion, usually consisting of skin, hair follicles, and sweat glands. It may slowly grow in size. This was ruled out in the current case because the mass was not cystic, and the biopsy was not suggestive of any skin or hair follicles. Hemangiomas are benign vascular tumors that usually present as reddish rubbery lesions on the skin, and do not present as a mass hanging from a pedicle. Teratomas are a type of germ cell tumor, most commonly found in the sacrococcygeal region, testis, and ovaries and usually do not present on the face; hence the diagnosis was unlikely. Therefore, the diagnosis in the current case was most consistent with fibroepithelial polyp.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the frequency of minor congenital anomalies.

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An Infant with Blue Spells During Feeding

Thomas Q. Gallagher, DO*

*Department of Otolaryngology-Head and Neck Surgery, Eastern Virginia Medical School, Norfolk, VA

Please view the barium esophagram (Fig 1) and watch the accompanying video clip (Video 1) showing the results of a flexible endoscopic evaluation of swallow (FEES) in a newborn.

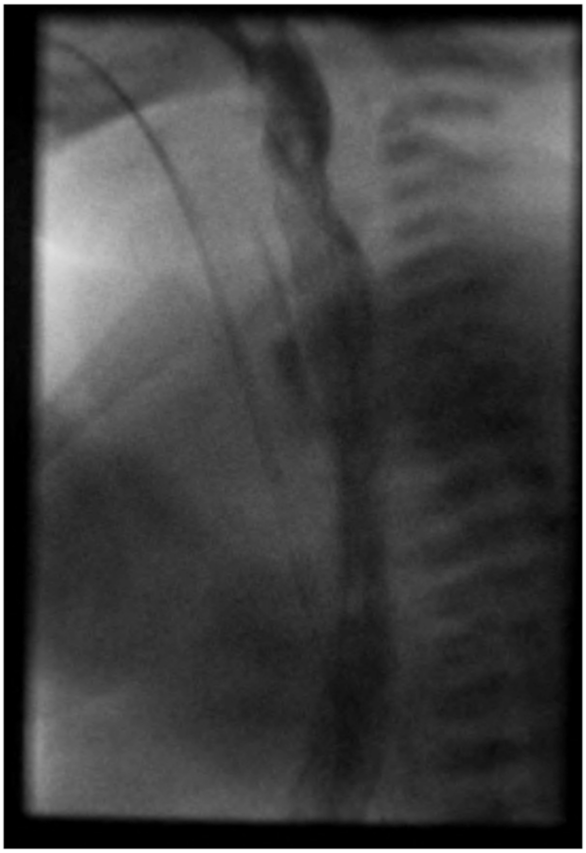
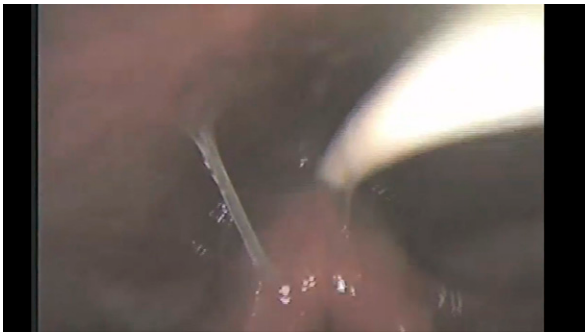


Figure 1. Barium esophagram lateral view (anterior to the left).



Video 1. The Results of a Flexible Endoscopic Evaluation of Swallow (FEES) in a Newborn.

AUTHOR DISCLOSURE Dr Gallagher has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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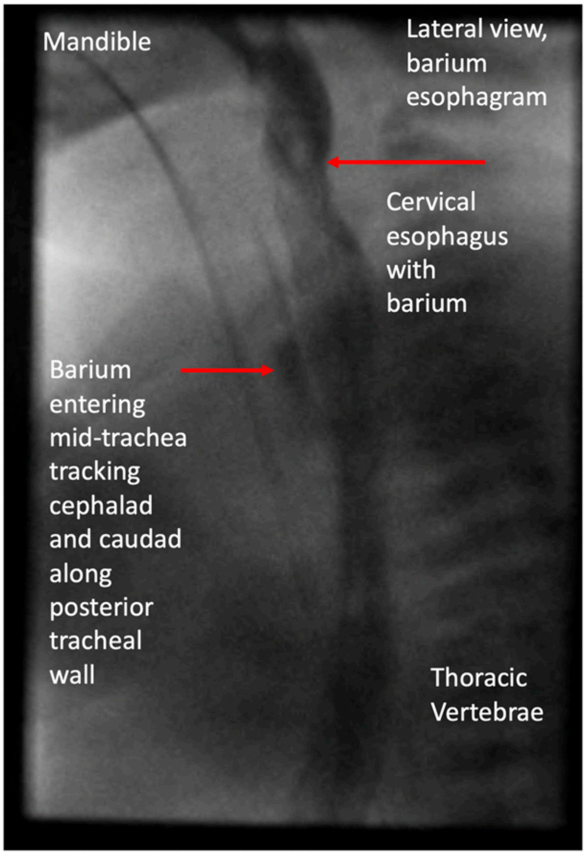
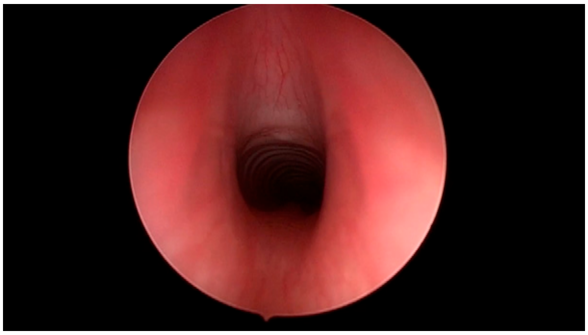

Mandible
Lateral view, barium esophagram
Cervical esophagus with barium
Barium entering mid-trachea tracking cephalad and caudad along posterior tracheal wall
Thoracic Vertebrae

Figure 2. Barium esophagram shown in Fig 1 with annotations. Attention was given to midtrachea extravasation of barium from esophagus. Barium is tracking cephalad along the posterior tracheal wall.

The most likely diagnosis of the neonate in this video is a(n):

A. Laryngeal cleft

B. Tracheoesophageal fistula



Video 2. Direct Laryngoscopy and Bronchoscopy of a Newborn.

C. Uncoordinated feed-suck-swallow reflex

D. Normal study

The female neonate depicted in Video 1 was born at term via vaginal delivery at 40 weeks and 2 days' estimated gestational age. The delivery was uncomplicated, and the neonate's Apgar scores were 8 and 9 at 1 and 4 minutes, respectively. She had a blue spell with oral feeding on the first day after birth and was transferred to the NICU for further observation. Subsequently, the neonate had several episodes, after oral feeding, of oxygen desaturations to the 50s associated with coughing with quick, spontaneous recovery. Currently she has a normal cry and no stridor. She does not have any respiratory issues aside from the feeding attempts.

Barium esophagography (Fig 2) demonstrates barium in the midtrachea but no evidence of "spill-over" from the glottis. This was initially read as normal with no evidence of tracheoesophageal fistula (note: this was later amended).

The otolaryngology service was consulted for further evaluation. At that time, a bedside FEES was performed in coordination with the feeding team.

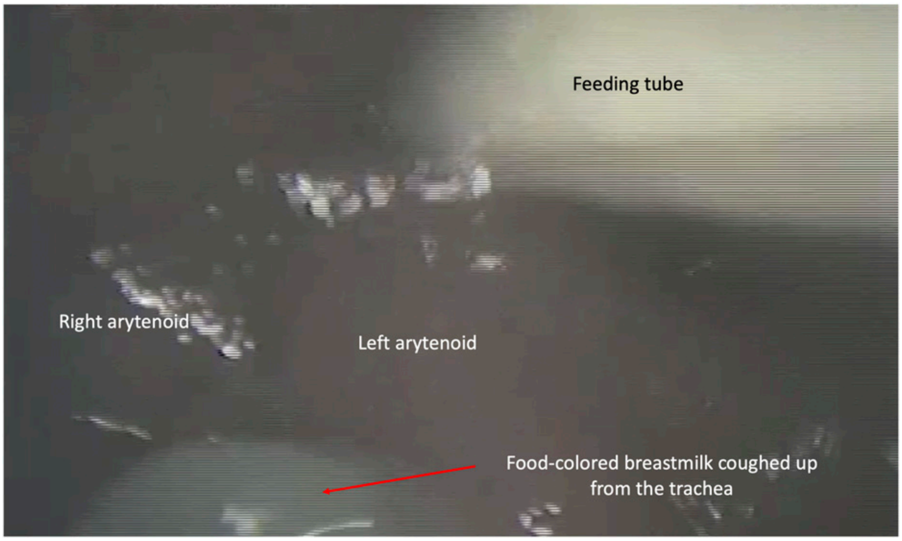


Figure 3. Still image from flexible endoscopic evaluation of swallow examination with annotations.

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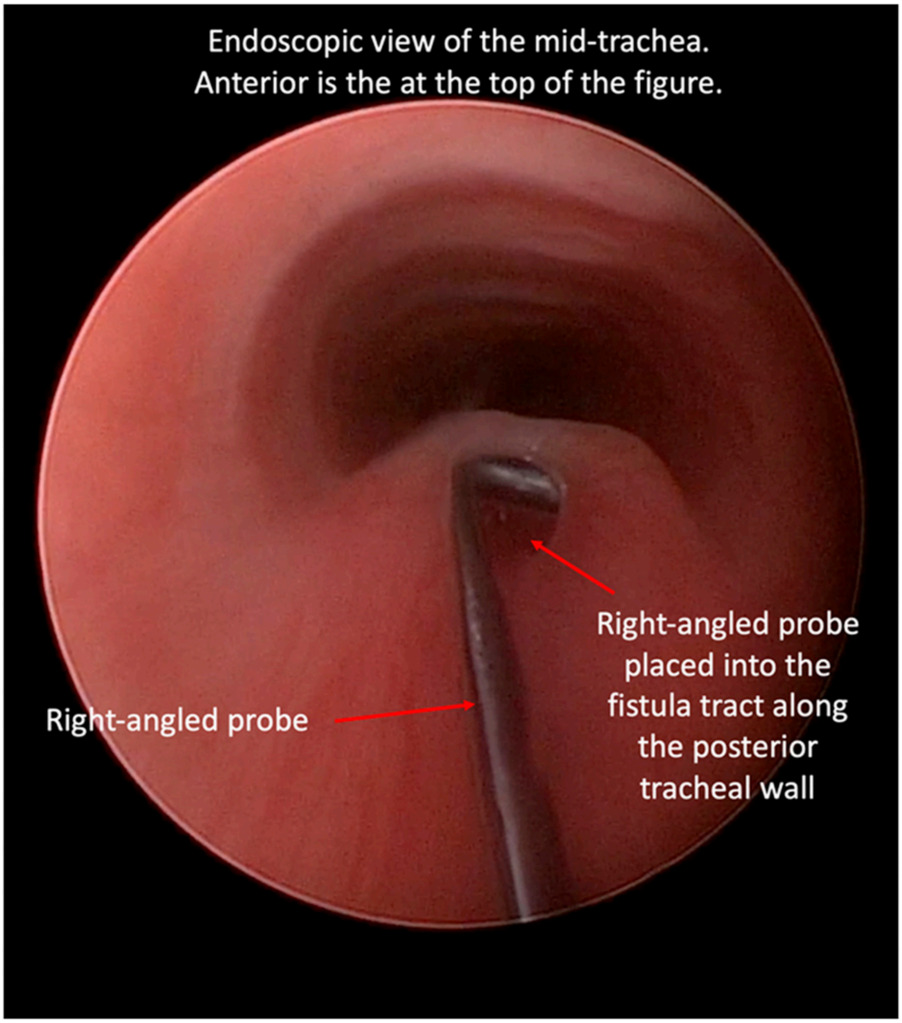
Endoscopic view of the mid-trachea.
Anterior is the at the top of the figure.
Right-angled probe placed into the fistula tract along the posterior tracheal wall
Right-angled probe

Figure 4. Still image from direct laryngoscopy/bronchoscopy with annotations.

We used a standard flow nipple and added green food coloring to the mother's expressed breast milk. The study (Video 1) demonstrated a normal suck-swallow-breathe with good pace and intake; however, after about 10 seconds of feeding, the neonate started coughing and choking with associated oxygen desaturations and cyanosis. The respiratory event was self-limited. During the coughing spell that followed, there was clear evidence of ejection of colored breast milk from the laryngeal inlet, indicating an occult aspiration event (Fig 3).

After this study, she was given nothing by mouth and taken to the operating room the next day for a formal direct laryngoscopy and bronchoscopy (Video 2). The results of the endoscopy demonstrated an H-type tracheoesophageal fistula (TEF). A guidewire was passed through the fistula (Fig 4) at the time of endoscopy to aid in identification during the time of open repair. The following day, the pediatric surgery team performed a successful open division of the fistula.

CRITIQUE

The FEES procedure is a method for assessing swallow function. It can be performed in adult and pediatric patients. The procedure is conducted at the bedside or in the clinic with a speech-language pathologist (SLP). Often, at institutions such as ours, an otolaryngologist performs the endoscopy and the SLP administers the feeding. However, at some institutions, this evaluation is conducted by SLPs. The benefits of this procedure over other swallowing evaluations such as videofluoroscopic swallow study (VFSS) is that it can be done without transferring the patients to the fluoroscopy suite, requires no radiation, and no barium is ingested. It provides direct examination of pharyngeal and laryngeal structures. In

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addition, it is the only instrumental examination that can be used to assess swallowing in a breastfeeding infant. (1) It has been shown to be of equivalent diagnostic value as VFSS. (2)(3)(4)(5)(6) Although FEES shows the pharyngeal phase of swallowing, one disadvantage of this study is that it does not provide views of the oral or esophageal phases of swallowing. One other characteristic of FEES is the "white out" that occurs during the pharyngeal squeeze portion of the swallow. Thus the clinician can view the bolus only before and after the swallow, and can infer the trajectory of the bolus during the swallow. (1)

An H-type TEF is a rare variant in the spectrum of congenital esophageal anomalies and consists of an isolated TEF in the absence of esophageal atresia. It accounts for approximately 4% of all cases of congenital esophageal anomaly, or about 1 in 87,000 births. (7) Patients with an H-type TEF present with choking during feedings, cyanotic spells, or recurrent pneumonias. Diagnosis can be made with radiography; however, endoscopy is the gold standard. An H-type TEF can be repaired via an open approach (cervical or thoracotomy depending on location) or endoscopically.

The FEES in this case showed clear signs of aspiration, indicating an abnormal study. A diagnosis of laryngeal cleft or uncoordinated swallowing are not consistent with this infant's findings because there was no evidence of barium in the proximal trachea. Rather, barium was noted only in the midtrachea.

CORRECT RESPONSE

B. Tracheoesophageal fistula, specifically, an H-type fistula, given that the patient did not have any associated esophageal atresia.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the various causes of stridor in the newborn and how to assess severity.

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ANSWER KEY FOR MARCH 2020 NEOREVIEWS

Inhaled Nitric Oxide in Emergency Medical Transport of the Newborn: 1.D; 2. E; 3. B; 4. C; 5. B.

Milrinone Use in Persistent Pulmonary Hypertension of the Newborn: 1. C; 2. A; 3. E; 4. C; 5. D.

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